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The Goulstonian Lectures

ON THE

SUPRARENAL BODIES.

Delivered before the Royal College of Physicians of London,

BY

H. D. ROLLESTON, M.A., M.D., F.R.C.P.,
Fellow of St. John's College, Cambridge; Assistant-Physician and Lecturer on Pathology at St. George's Hospital.

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LECTURE I.

THE ANATOMY, HISTOLOGY, AND MORBID ANATOMY OF THE SUPRARENAL CAPSULES.

[In his preliminary remarks the lecturer thanked the College for the honour conferred on him, and said that since the suprarenal capsules were attracting considerable attention at the present time, it seemed opportune to review the state of our knowledge concerning them.]

Method of Removal.—It may, perhaps, not be out of place to say a few words about the method of examining the suprarenal capsules *post mortem*. In ordinary cases they should not be removed at the same time as the kidneys, but the following plan should be adopted: After the lungs, intestines, stomach, duodenum, and pancreas have been removed, the connective tissue should be dissected from the upper and inner border of the left kidney; by this means the left suprarenal will be exposed *in situ*, and can then be easily removed.

In order to satisfactorily expose the right suprarenal body the liver should not be removed, but should be allowed to fall back into the empty thorax. To effect this the diaphragm must be freely cut across. This upward rotation of the anterior margin of the liver puts the inferior vena cava on the stretch. After opening the inferior vena cava it should be picked up with forceps, and dissected off the spine; in this way the right suprarenal capsule is completely exposed *in situ*, and can then be easily removed with a little dissection. If the liver is taken out first, the capsule, from their close relations, is often removed with it, or cut in half.

THE RIGHT SUPRARENAL CAPSULE.

The right suprarenal capsule embraces the inner, upper, and anterior part of the corresponding kidney. Its outline, as seen from the front, is roughly triangular, with angles pointing respectively (1) outwards, (2) upwards, and (3) downwards. It is flattened and presents two surfaces, anterior and posterior, each of which is divisible into two secondary areas.

The anterior surface is not uniformly flat; along its upper and inner borders there is a continuous depressed area. This bears a varying proportion, one-third to a-half, to the whole extent of the anterior surface, usually about a third. The two areas thus formed on the anterior surface are separated by a furrow. The furrow is overhung by the margin of the larger, outer, and comparatively elevated area.

Section of the suprarenal capsule shows that the furrow corresponds to a projection on the posterior surface.

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This undulation on the anterior surface follows the curve of the upper and inner borders. At a point on this undulation, corresponding to the upper and inner angle, the suprarenal vein issues from the medulla in the furrow, and runs upwards to enter the inferior vena cava.

The depressed area is uncovered by peritoneum; the part which lies adjacent to the upper border is in immediate contact with the right lobe of the liver, while that part which corresponds to the inner border lies underneath the inferior vena cava.

The remaining or elevated area on the anterior surface presents (1) a non-peritoneal portion (Anderson)[1] for the hepatic flexure of the duodenum near its lower angle; the extent of this portion varies very considerably (St. John Brooks);[2] and (2) a portion covered by the peritoneum forming the hepato-renal fold.

The posterior surface is divided by a projection into two secondary areas. This projection, which is the counterpart of the furrow on the anterior surface, fits into the groove between the kidney and the right crus of the diaphragm. This undulation in the suprarenal body is oblique, and the process on the posterior surface looks outwards. Of the two secondary areas the inner is flattened by the pressure of the right crus of the diaphragm, and is larger than the outer area, which is so tilted upwards by the underlying kidney that it looks backwards and downwards. These two secondary areas do not lie in the same plane, and in early life appear so distinct as to suggest a description of three surfaces to the right suprarenal body—namely, an anterior, corresponding to that described above; a posterior, in contact with the crus of the diaphragm; and an inferior, in contact with the kidney. As age advances, however, the suprarenal becomes thicker, and the tripartite appearance is less marked.

On comparing the secondary areas on the anterior surface with those on the posterior surface, it is seen that on the anterior surface the outer area is the larger, and overlies the smaller outer area on the posterior surface, while the smaller inner depressed area on the anterior surface corresponds to the larger surface for the crus on the posterior surface. The difference in size of corresponding areas on the two surfaces depends on the obliquity of the undulation. The presence of this undulation and its obliquity appear to be mechanically explained by the pressure exerted on the suprarenal capsule by the adjacent organs. Thus the immediate contact of the liver and inferior vena cava with parts of the anterior surface tend to fix that area, while the kidney from behind presses the rest of the anterior surface forwards, and slightly towards the middle line. The groove between the right crus and the kidney readily receives part of the organ, and is responsible for the spur-like process on the posterior surface.

THE LEFT SUPRARENAL CAPSULE.

The left suprarenal capsule is applied to the inner margin of the upper half of the left kidney, which it overlaps; it passes into the upper margin of the kidney for a short distance only. The inner border is convex, and looks slightly upwards; the outer border is concave. There are two angles: the upper which is pointed, and the inferior rounded and covering the renal vessels. There are two surfaces—anterior and posterior. The anterior has a crescentic outline. It is flat, and traversed by a groove or furrow, from which the suprarenal vein runs downwards to join the left renal vein. This groove runs from above downwards and inwards, and thus divides the anterior surface into two secondary areas: (*a*) an outer and inferior, and (*b*) an inner and upper. Near the superior angle these areas are of equal size, but below the outer becomes the larger, and forms the lower rounded angle of the suprarenal body.

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[1] Morris's *Anatomy*, p. 1050.

[2] Cunningham's *Manual of Practical Anatomy*, p. 505.

Relations of the Anterior Surface.—The anterior surface is divided into (1) an upper portion covered by the peritoneum of the lower sac, and in relation with the cardiac end of the stomach near the entrance of the œsophagus, and below that with the superior extremity of the spleen; and (2) the lower part uncovered by peritoneum, and in direct contact with the pancreas and splenic artery. On the posterior surface there is a projection corresponding to the furrow on the anterior surface. This projection passes between the kidney and the crus of the diaphragm almost at right angles to the plane of the anterior surface. This undulation is vertical, thus contrasting with the oblique undulation in the right suprarenal body. External to the projection there is the external area larger than the internal. This external area is thin, and is expanded by the pressure of the underlying kidney. The renal vessels as they pass into the hilum lie under cover of this area. Internal to the projection is the smaller internal area which rests on the crus of the diaphragm; it is thick and compact, and may cover the left semilunar ganglion, but this is not a constant relation.

ANATOMICAL CONFORMATION.

The different folding, as shown by the oblique and vertical directions of the undulations respectively in the right and left suprarenal bodies, depends on the differences in the packing of the two organs. The probable explanation of the more complicated form of the undulation on the right side is the close relation to the firm liver, and the pressure thereby exerted on the suprarenal body. The right suprarenal body is flattened and expanded, while the left is compact. Occasionally the right may be more compact and resemble the left, while again the left may be somewhat expanded and flattened. Each of the organs weighs about a drachm or rather more, the left being rather the heavier.

In cases where the kidney is displaced, the corresponding suprarenal capsule remains in its normal position. When a horseshoe kidney exists the position of the suprarenal bodies undergoes no change, even though the kidney is situated over the promontory of the sacrum. In an example of this kind the suprarenal bodies lay on the crura of the diaphragm, and were flat and not thrown into their normal undulations. This observation shows the influence which the pressure normally exerted by the kidneys has on the conformation of the adrenals.

The suprarenal body has a firm capsule of fibrous tissue, and running in from it are septa containing small arteries which traverse the cortex and reach the medulla. To the naked eye the section of the suprarenal body shows an outer buff layer or cortex surrounding the grey to dark-brown central part or medulla, in the centre of which there is a greyish-white area containing one or more large veins. The colour of the medulla varies considerably.

The arteries derived from the aorta, renal and phrenic arteries, enter the cortex and pass inwards towards the medulla: at the hilum the cortex thins away and exposes the medulla, from which the suprarenal vein issues.

The suprarenal vein in the medulla is surrounded by large bundles of smooth muscular tissue, which form a prominent feature on section. Guarnieri and Magini[3] suggest that the circulation through the organ may be slowed by the contraction of these muscular bundles.

In fœtal life the large and very vascular suprarenal capsules are relatively, though not absolutely, larger than in adult life. Their large size and vascularity make it probable that their functions are more extensive and active in fœtal life. At the third month of intrauterine life the kidneys and suprarenal capsules are of the same size; at the sixth month the kidneys are twice the size of the suprarenal capsules and more than twice their weight. At birth the kidneys are about three times heavier than the suprarenal capsules, while in adult life, the kidneys weighing on an average 5½ ounces and the suprarenal bodies 1 drachm each, the relation is 44 to 1. After birth the suprarenal capsules continue to increase in size, and, like other organs, attain a size varying roughly with that of the whole body. At what time they cease to grow it is impossible to say; but the general impression left on my mind from examining more than 1,000 pairs is that they are larger about 40 years of age than at other periods of life. Probably some of the increase in size is due to fatty change. Their growth after birth shows that they cannot be regarded as mere fœtal relics. In old age they diminish in size and, like other parts of the body, contain less fat.

It is often stated that the suprarenal bodies are larger in negroes than in the white races. Duckworth[4] mentions five dissections of negroes in which the suprarenal capsules were not larger than in whites. Professor Macalister has kindly informed me that in four negroes and in one Malay dissected by him the suprarenal bodies presented no unusual features.

ABNORMAL SUPRARENAL BODIES.

The different shape of the two suprarenal bodies depends on their different relations and packing. I have seen the left expanded, and the right approaching the shape of the left. It would be natural to suppose that in transposition of the viscera the respective forms of the two would also be reversed.

I have met with abnormal projections from the suprarenal body on both sides. The figure, from a photograph kindly done by Mr. W. Paul Jones, shows one on the right side. If more pedunculated it might resemble in appearance an accessory suprarenal body.

In anencephaly and hemicephaly the suprarenal capsules may be atrophied or absent; on the other hand, they may be normal. Alexander[5] has not been able to find any cases of fœtuses in which atrophy of the suprarenal bodies was associated with a normally developed brain and spinal cord.

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[3] *Archiv. de Biologie*, Tome x, fascic. iii, p. 383.

[4] *St. Bartholomew's Hospital Reports*, vol. i, p. 225.

Zander[6] attributes the atrophy of the suprarenal bodies to the maldevelopment of the nervous system; while Alexander considers that the primary lesion is in the suprarenal bodies, and that suppression of their function is one, among several, of the causes influencing the development of the central nervous system. This view is of considerable interest in connection with the severe lesions which Tizzoni found in the brain and spinal cord as a result of removal of the suprarenal capsules.

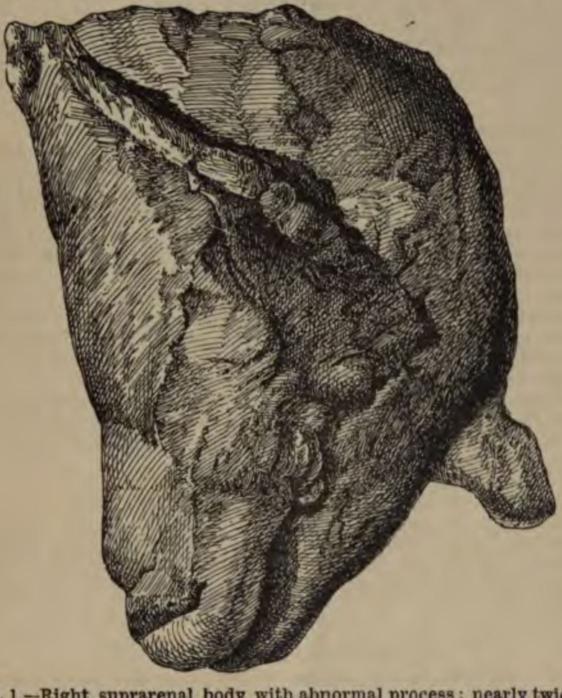

Fig. 1.—Right suprarenal body with abnormal process; nearly twice natural size.

ACCESSORY SUPRARENAL BODIES.

Accessory suprarenal bodies are very commonly present in the connective tissue in the immediate neighbourhood of the two organs. They are found when looked for, but do not otherwise, as a rule, attract attention, as they are so small. They are yellow in colour, oval or round, and usually about the size of a grain of corn. They are often in contact with the main organ, or may be attached to it by tags of fibrous tissue, of various lengths, containing small vessels. Sometimes irregular processes come off from the surface or edge of the suprarenal capsules. If the base of these projections becomes constricted an accessory suprarenal will result. These projections are different from the small adenomata so commonly met with in adults in which fatty degeneration is always a prominent feature.

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[5] *Ziegler's Beiträge*, vol. xi, 1892. [6] *Ziegler's Beiträge*, vol. vii, 1890.

The number of accessory suprarenal bodies varies. I have seen as many as five on one side (the right), but this was in a case in which that capsule contained caseous material, so their presence may have been the result of some compensatory hypertrophy taking place, especially as the case was that of a boy of 17 years dying of chronic phthisis without any symptoms of Addison's disease. Stilling[7] has shown that hypertrophy of accessory adrenal bodies may take place in young animals after the experimental removal of the organs. Although there is no evidence of compensatory hypertrophy occurring in adult man, it is possible that it may occur in early life. The largest accessory suprarenal I have seen was as large as a cherrystone, and was attached by a loose tag of connective tissue to the right suprarenal.

The accessory suprarenal bodies may be found among the fibres of the renal or solar plexus and in close relation to the semilunar ganglia. It is said that accessory suprarenal bodies may occur in the substance of the main organ, but it is probable that the structures observed were adenomata or portions of a much convoluted suprarenal body cut in section. The presence of accessory suprarenal bodies in such distant parts as the broad ligament of the uterus and along the course of the spermatic vessels was pointed out by Marchand,[8] and explained on embryological grounds. Examples of accessory adrenal bodies on the spermatic vessels near the inguinal canal are quoted by Schmorl.[9]

Structurally the larger accessory suprarenal bodies show a division into cortex and medulla, while in the smaller ones this is not the case.[10] In children the cells are not pigmented, while in adults pigment is present.

SUPRARENAL "RESTS."

Instead of being in the loose connective tissue, accessory suprarenal bodies may be found embedded in the kidney or liver, and are then often spoken of as suprarenal "rests," They are more commonly recognised in the kidney than in the liver, though Schmorl records four examples of suprarenal "rests" occurring in the liver in 510 examinations. In these four cases the "rests" were in the right lobe of the liver. This writer thinks it probable that the liver tissue surrounds the accessory suprarenal bodies, as in two of his four cases the right kidney was displaced, and the resistance to the growth of the right lobe of the liver, normally due to the adjacent kidney, was absent.

In the kidney suprarenal rests appear in two forms: (1) The commoner, small round masses embedded in the cortex, and often so extensively degenerated into fat, that they have been called "renal lipomata."[11] They resemble the dried-up cysts not uncommonly seen on the cortex of the kidney. Like the suprarenal rests in the liver they may be multiple.

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[7] *Virchow's Archiv*, quoted by Boyce in *Path. Histology*, p. 239.

[8] *Virchow's Archiv*, Bd. xcii.

[9] *Beiträg. z. path. Anatom. Ziegler*, vol. vi, 1889.

[10] Duckworth, *St. Bartholomew's Hospital Reports*, vol. i.

[11] Grawitz, *Virchow's Archiv*, Bd. xciii.

They occur in any part of the cortex of the kidney. Histologically they have been described as conforming in different cases to the type of each of the three zones in the cortex of the suprarenal capsule, or even to the medulla. (2) Flattened plaques of suprarenal tissue, the medulla being represented as well as the cortex, which are placed partly inside, partly outside, the capsule of the kidney. Dr. Newton Pitt[12] has described this condition on both sides; I have seen it on one side. This condition occurs in the upper part of the kidneys, where pressure is exerted by the liver and spleen. The pressure probably flattened out the accessory suprarenal bodies or rests, so that the difference in form of these two varieties is due to their respective positions. Just as the more expanded condition of the right suprarenal body is explained by the fact that it is more tightly packed than the left, which is much more compact. In some animals the suprarenal body is round or oval, just as are the common accessory adrenals in man.

THE HISTOLOGY OF THE SUPRARENALS.

The Cortex.—The cortex is usually described as consisting of an outer zone (the zona glomerulosa), lying internal to which are the zona fasciculata and the zona reticularis; between the latter and the medulla no hard and fast line can be drawn. The cells found in the cortex are large epithelial cells, which have been compared by Creighton[13] to the cells in the stratum granulosum of a Graafian follicle. The cells in the outer part of the cortex are larger than those in the inner, the transition being a gradual one. The arrangement of the cells, especially in the zona glomerulosa, has suggested the idea that there are capillary ducts between the cells, but nothing very definite can be made out. The radial arrangement of the cells in the cortex probably depends on the septa, blood vessels, and lymphatics running inwards towards the medulla.

The cells of the cortex very readily become occupied with large globules of fat; this is so commonly met with in adults as to be considered normal. The presence of extensive fatty change and the much smaller relative size of the suprarenal capsules to the rest of the body in adult life make it probable that the function or functions discharged by them are more active in fœtal life.

HISTOLOGY.

Ganglion cells are described as being sometimes seen on the outside of the cortex, but are never present in the substance of the cortex. In a section shown me by my friend Dr. Morley Fletcher there was a collection of ganglion cells inside the capsule of the organ. In the inner part of the cortex small vascular dilations may be seen between the cells.[14]

The cells in the innermost layers of the zona reticularis are granular, and stain brown with chromic salts; they resemble the cells of the medulla, and contain a varying amount of pigment. The presence of granules in the cells is of interest, as they are possibly the precursors of a material secreted by the cells—a zymogen, analogous to that of secretory glands. In negroes the cells of the cortex are said to be extensively pigmented.

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[12] *Path. Trans.*, xlv, p. 141, 1894.

[13] *Journal of Anat. and Phys.*, Oct., 1878.

[14] Guarnieri and Magini, *Archiv. Italien. de Biolog.*, Tome x, Fasc. III.

Canalis[15] has observed indirect nuclear division in the cortex of adult animals, and concludes from this that the suprarenal bodies remain functionally active. By the kindness of Dr. Hill, Master of Downing College, Cambridge, I am allowed to mention his, as yet unpublished, opinion that from active mitosis occurring in the deeper layers of the zona reticularis, it appears probable that the growth of the adult suprarenal capsule occurs in that situation, and that the cells pass outwards to form the cortex, and inwards to form the medulla. Gottschau[16], however, believes that the cell formation goes on in the zona glomerulosa and outer part of the zona fasciculata, and that the destruction of cells which takes place in the zona reticularis and medulla provides some substance of unknown function, which passes into the blood.

The extreme frequency with which a fatty condition of the outer part of the cortex is met with, makes it somewhat improbable that these cells are responsible for the growth of the organ. These facts, together with the absence of karyokinesis from the medulla,[17] make it highly probable that the suprarenal body grows from the zona reticularis.

THE MEDULLA.

The medulla is not present in the whole of the suprarenal body; at the expanded margins the cortex turns on itself, and there is no medulla. The cells of the medulla are of different forms; some of them appear to be branched, but their outlines are far from easy to make out. A rodded appearance of the cells, like that seen in the convoluted tubes of the kidney, has been described by Guarnieri and Magini.[18] The cells of the medulla are granular, but in unstained sections examined by transmitted light the medulla appears lighter than the cortex, owing to the latter being so extensively infiltrated with fat.

When fresh the cells of the medulla stain brown with bichromate of potassium. This reaction is only obtained soon after death; it becomes less marked as the interval increases, until, twelve hours after death, it is completely lost. Stilling[19] describes these cells as chromophile, and in animals he finds them in the sympathetic and intercarotid gland as well as in the suprarenal body. These cells stain blue with persulphate of iron.

The brown reaction with chromic salts of the cells of the medulla has long been known; it appears to have been first pointed out by Henle. Creighton[20] says that this coloration affects the nuclei and also the blood in the lacunar spaces between the cells of the medulla, while recently Manasse[21] has noticed in suprarenal bodies hardened in Müller's fluid homogeneous, brown material in the veins, which he traced to its origin in the cells of the medulla. These appearances could not be made out in specimens hardened in spirit, as spirit dissolves this "hyaline" material. Auld[22] regards the medulla as a tubulo-alveolar gland, and describes colloid matter as being present in its acini at rare intervals. If these acini are in reality blood spaces, the colloid material described by him, and the hyaline casts of Manasse, would appear to correspond to each other.

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[15] *International Monatschrift-Krause*, vol. iv, 1886.
[16] *Archiv Anat. u Entwick.*, Leipzig, 1883, p. 456.
[17] *International Monatschrift-Krause*, vol. iv, 1886.
[18] *Archiv. Ital. de Biolog.*, Tome x, p. 382.
[19] *Rev. de Méd.*, 1890.
[20] *Loc. cit.*
[21] *Virchow's Archiv*, Bd. 135, Heft. 2, p. 263.

Guarnieri and Magini describe cylindrical bodies with a refractile index between, or more often inside, the cells of the medulla, which do not appear to be fat, and which may be the same as the bodies described by Auld and Manasse.

The cells of the medulla do not become so readily infiltrated with fat as those of the cortex, but they certainly do to a minor degree, though Alexander considers that very possibly the particles are not fat, but something else.

Virchow describes a pink coloration of the medulla on adding a solution of iodine, which disappeared on adding sulphuric acid. C. Alexander[23] describes a similar reaction in the zona glomerulosa, which is not affected by the further addition of sulphuric acid.

Orth refers to a green coloration of the medulla on adding a solution of perchloride of iron as a sign of chromogen in the cells of the medulla.

Much discussion has taken place as to the existence of ganglion cells in the medulla. The varying appearance of the cells in the medulla offer considerable opportunities to the imagination. These are all transitions between typical epithelial cells and cells which, if met with elsewhere, would be described as ganglion cells. Leydig and Luschka considered the cells of the medulla to be nerve cells. Virchow and most writers describe ganglion cells as being present. Auld describes ganglion cells and modified ganglion cells. Holm[24] has described large cells with large nuclei, which he calls "doubtful ganglion cells"; they are, however, probably the groups of epithelial cells found surrounding grey nerve fibres described by Guarnieri and Magini.[25]

Alexais and Arnaud,[26] and Guarnieri and Magini,[27] deny the existence of any nerve cells in the medulla.

Probably there are some few ganglion cells in connection with the numerous grey nerve fibres present in the medulla, which form a network, and have in places groups of epithelial cells surrounding them; in their description of these non-medullated nerve fibres Guarnieri and Magini say they have never been able to find their termination. Fusari,[28] using Golgi's silver nitrate method, has found a delicate fibrillar termination of the nerve fibres between the cells.

The medulla contains a reticulum of connective tissue, in which lie epithelial cells and blood sinuses with thin walls, which receive the blood from the arterioles of the cortex, and eventually open into the central vein. The vessels of the suprarenal capsules, with the exception of the central vein, have thin walls composed of little more than endothelium. Lymphatic vessels have been described between the cells.

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[22] BRITISH MEDICAL JOURNAL, October 6th, 1894.

[23] *Ziegler's Beiträg.*, vol. xi, No. 7.

[24] *Sitzungsber. der Wiener Acad. der Wissenschaft*, 1886.

[25] *Archiv. de Biologie*, Tome x, p. 282.

[26] *Rev. de Méd.*, Paris, 1891, p. 315.

[27] *Loc. cit.*

[28] *Archiv. Ital. de Biolog.*, xvi, p. 262.

The blood spaces are surrounded by the cells, so that there is some resemblance to the arrangement in the liver of cells and capillaries; Manasse has described groups of cells projecting into the lumen of the veins, and pouring out, as a kind of secretion, brown hyaline matter.

What is the significance of these appearances? MacMunn[29] has put forward the view that the function of the suprarenal bodies is to remove effete blood pigment from the circulation. Delépine,[30] in an article on the normal storage of iron in the liver, says that from the destruction of red blood corpuscles in various parts of the body a soluble albuminous ferruginous substance results, and is carried to the liver, where this compound is decomposed and iron stored up for a time in the peripheral part of the lobules of the liver. From the point of view that a katabolism of blood pigment does occur in the medulla of the suprarenal, it is possible that the material described by Manasse is the albuminous ferruginous compound described by Delépine. But, as will be seen later, there is no proof that destruction of red blood corpuscles, or metabolism of effete blood pigment, does occur in the suprarenal bodies.

Relation of the Cortex and Medulla to Each Other.

At the present time the cortex and the medulla of the suprarenal body are generally considered not to have the same relation to each other as they have in a lymphatic gland, but to be distinct in origin, structure, and function. The cortex is regarded as being glandular or hæmatopoietic, and the medulla as being nervous and connected with the sympathetic. This view—held by Kölliker—is the one expressed in the standard textbook of *Physiology* by Foster.[31]

From an embryological standpoint Balfour and Mitsukuri[32] have shown the medulla to be connected with the sympathetic, and the cortex to be derived from the mesoblast. Weldon[33] considers the suprarenal cortex to be derived from the Wolffian bodies, and that it secondarily encloses blood vessels and nerves to form the medulla.

Mitsukuri lays stress on the presence of nodules in the medulla, which he regards as the remains of the sympathetic rudiment of the medulla. Minot[34] is unable to recognise their presence before the second month or after the seventh month of intrauterine life. These nodules disappear, so that even if the medulla is embryologically connected with an ingrowth of the sympathetic the sympathetic rudiment does not persist, and the medulla as well as the cortex is formed eventually from the inter-renal body (mesoblastic) described by Balfour.

In connection with the view[35] that the adrenal bodies are derived from the germ epithelium, the observations of Creighton[36] are interesting. In the cortex of the horse and of the dog he occasionally found tubes resembling the aborted Graafian follicles of the ovary; he therefore divides the suprarenal body into two parts—these tubes in the cortex, and the remainder (which consists of ordinary medulla and most of the cortex). These tubes degenerate and pass into the ordinary cortex—in the horse fading into the zona fasciculata, in the dog into the zona glomerulosa. These tubes correspond to the follicles in the cortex of the ovary, while the remainder corresponds to the stratum granulosum in the corpora lutea and to the interstitial cells of the ovary.

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[29] British Medical Journal, February 4th, 1888.

[30] *Practitioner*, 1890, p. 84.

[31] Foster, *Physiology*, Book ii, p. 765, 1889.

[32] *Quarterly Journ. Microscop. Science*, vol. xxii, 1882, p. 17.

[33] *Quarterly Journ. Microscop. Science*, April, 1884.

[34] *Human Embryology*, p. 487.

[35] Janosik, *Arch. f. Microscop. Anat.*, Bd. xxii, 1883.

[36] *Loc. cit.*

The distinction between the cortex and medulla of ordinary anatomy Creighton considers quite arbitrary, as there is no real difference between their constituent cells. The central part or medulla is only more spongy than the rest. Arnold[37] considers the difference between the cortex and medulla as being due to modifications in the arrangements of the interstitial supporting tissue and of the blood vessels, and draws attention to groups of cells near the central vein which closely resemble the zona glomerulosa.

At the sixth month[38] of intrauterine life there is no difference between the cortex and the medulla, if the sympathetic nodules which are about to disappear be excluded, and on the microscopic examination of the adult organ the transition is seen to be very gradual.

From these considerations I should be inclined to regard the suprarenal as a functional whole, the medulla and cortex performing the same work, though possibly in unequal degrees, since the cortex very commonly undergoes considerable fatty change. This speculation, based on anatomical grounds, receives strong support from the observation that the medulla alone provides an active extract.[39] The character of the epithelial cells would quite support the view that the function of the suprarenals is the elaboration of some secretion, which, like that of the thyroid gland, is carried off by the lymphatics or veins for some use in the economy.

VARIOUS MORBID CONDITIONS OF THE SUPRARENAL BODIES.

Although the sketch of the physiology of the suprarenal bodies would naturally come after their histology, it is more convenient to refer to the chief lesions of morbid anatomy affecting them before considering the functions of the suprarenal bodies, since that subject was so closely connected with the explanation of Addison's disease.

ATROPHY.

How often atrophy of the suprarenal capsules occurs does not seem to have been investigated, and its presence is only recorded when there were indications of Addison's disease during life. The suprarenal capsules normally diminish in size in advanced life. In an examination of the organs in 1,050 *post-mortems* I found them small in 6 cases under the age of 45; in 3 both were small, and there were no signs suggesting Addison's disease; in 1 case there was caseation in the right and atrophy of the left without any symptoms; and in 2 cases of phthisis, where there was slight pigmentation, the suprarenal bodies were small. I have never seen the extreme degree of atrophy described in some cases of Addison's disease in which the organs were reduced to the size of peas.[40]

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[37] *Virchow's Archiv*, Bd. xxxv, S. 84.

[38] Observation by Dr. A. Hill, not published.

[39] Schäfer and Oliver, *Proc. Phys. Soc.*, March 16th, 1895.

[40] *Vide* Lecture II.

HÆMORRHAGE INTO THE SUPRARENAL CAPSULES.

As the result of severe injuries, such as fracture of the spine or rupture of the liver and spleen, blood is often poured out around the suprarenal bodies. Hæmorrhage into the suprarenal bodies is not infrequently met with under these conditions; the extravasation is almost always into the medulla.

As the result of traumatism during birth hæmorrhages frequently occur into the suprarenal capsules. On an examination of 130 stillborn children Dr. H. Spencer[41] found extravasations into these organs in 26; in 2 of these the hæmorrhage occurred in the cortex, in the remaining 24 it was into the medulla, and in half the cases it was bilateral; in 3 cases the hæmorrhage had ruptured the capsule. These hæmorrhages occurred more often in difficult labours, and were more frequently met with in pelvic than in cephalic presentations.

The question as to what changes take place in the suprarenal capsules as a result of such extravasations, if the child lives, is an interesting one. Wainwright[42] has recorded the case of a child 2 months old in whom the suprarenal bodies showed changes which were probably due to imperfect absorption and organisation of blood extravasated into the medulla. It is possible that organisation of extravasated blood might finally result in the cirrhotic atrophy of the adrenals, which, when bilateral, has been associated with the symptoms of Addison's disease. Unilateral atrophy with a fibrous increase, which is sometimes met with accidentally, could thus be explained by a former unilateral hæmorrhage.

Speaking on visceral hæmorrhages in stillborn children, Mr. Doran[43] said that possibly sarcoma in infancy might sometimes develop in association with these hæmorrhages.

Apart from traumatism hæmorrhage into the medulla of the suprarenal capsules has been recorded in a variety of conditions, in which the most common factor is venous congestion. In a few cases hæmorrhage has been associated with definite symptoms, such as pain in the back, or even with those of Addison's disease.

CLOUDY SWELLING.

Softening and cloudy swelling of the suprarenal capsules occur in febrile conditions, and it is noteworthy that the spleen and the adrenal bodies show very similar changes under these conditions. The medulla appears sodden and blood-stained, and microscopically small extravasations may be found in the cortex. The softening often leads to a separation between the cortex and the medulla, and thus produces an apparent cavity. This ancient observation finds a permanent record in the term "capsule."

In pyæmia small vascular streaks in the cortex, or more rarely minute abscesses, due to embolism, may occur. In pyæmia set up experimentally in guinea-pigs, Langlois and Charrin[44] have described swelling and hæmorrhages in the suprarenal bodies. Swelling and congestion have similarly been observed in animals inoculated with Klebs-Loeffler bacillus and other specific micro-organisms.

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[41] *Obstetrical Trans.*, 1892, p. 276.
[42] *Pathol. Trans.*, vol. xliv, p. 137.
[43] *Obstetrical Trans.*, 1892.
[44] Quoted *Lancet*, August 19th, 1893.

FATTY CHANGE.

Fatty change is so commonly met with in the suprarenal bodies of adults as to be generally considered a normal condition, while in young children these organs have hitherto been thought to be free from fat. The fat occurs as large globules in the cells. This change may be present throughout the whole of the cortex, or be best marked in the zona fasciculata. The medulla is occasionally seen to be occupied by fat, but never to the same extent as the cortex. Attlee,[45] in a paper as yet unpublished, has recorded the results of the examination of the suprarenal bodies in infants.

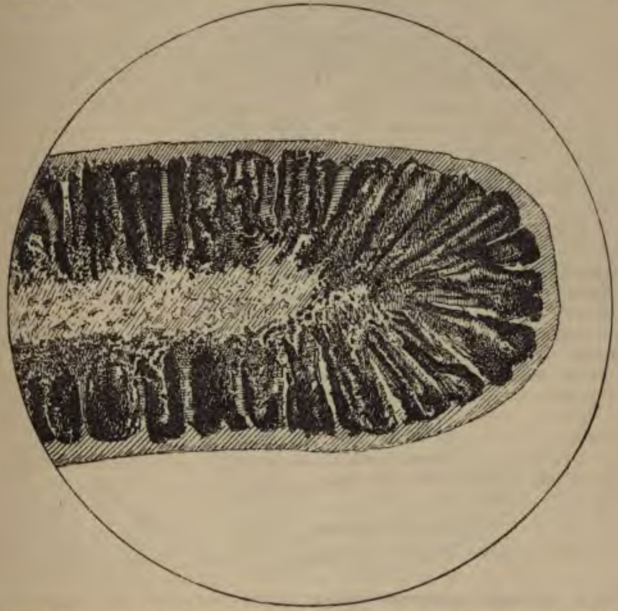

Fig. 2.—Suprarenal body stained with osmic acid showing extensive fatty change. Marasmic infant. Low power.

In marasmic infants the suprarenal bodies were found to be extremely fatty (Fig. 2), and to have undergone this change more constantly than the liver. Thus in nine cases the cortex showed fatty change in all, and in six of them the medulla was also affected, while in eight of these cases in which the liver was examined it was found to be affected in four and normal in the other four.

In stillborn children, on the other hand [illegible]
found to be very moderate in degree [illegible]

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[45] Act for M.D.Cambridge, from Patholog [illegible]
mew's Hospi [illegible]

with that seen in marasmic children, while in children dying from diseases other than marasmus fatty change was found, but not to the same extent as in that condition. As far as my observations go, they agree with these results. (I am indebted to Dr. Attlee for Figs. 2 and 3).

Experimentally, Attlee found that in young rabbits in which the suprarenal bodies normally are free from fat, starvation gave rise to marked fatty changes in these organs, and that here, as in marasmic infants, the liver might escape. Martinotti[46] made the curious observation that starving guinea-pigs for three or four days increased the normal amount of karyokinesis in the cortex. In adult rabbits the suprarenal capsule may normally show considerable fatty change, but starving, extensive suppuration, and poisoning, whether acute or chronic, appeared to give rise to marked fatty change.

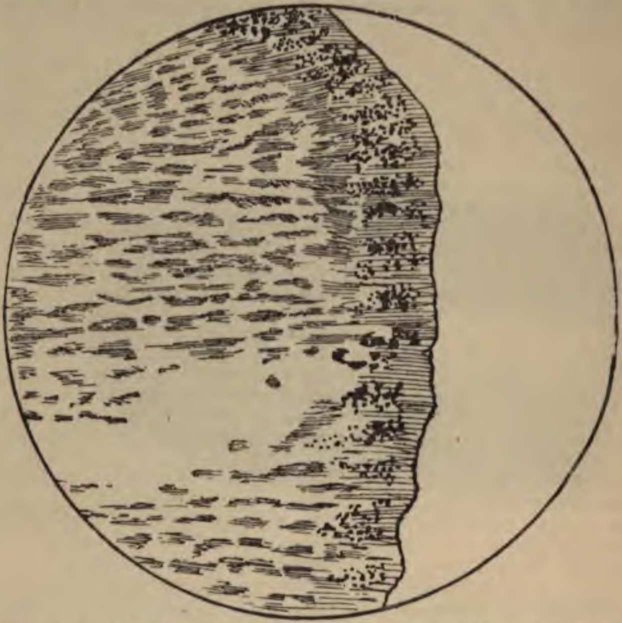

Fig. 3.—Cortex of suprarenal body from stillborn child, very little fat. High power.

With regard to these changes two questions arise (1) what is the nature of the change, and (2) what is the significance of its occurrence? Is the change to be considered as a storage of fat of the same kind as the fatty infiltration in the liver, or is it to be regarded as a degeneration of the cell protoplasm, due to the action of some poison conveyed to the suprarenal body by the blood?

The large size of the fatty globules, the distribution of the fat in the cortex, which, since this area receives the blood first from the branches of the suprarenal arteries, may be thought to be analogous to fatty infiltration of the liver, and the frequent association of fatty infiltration in the liver and subcutaneous tissues (obesity) points rather to its being a storage or infiltration of fat. The occurrence after experimental poisoning and in marasmus, on the other hand, would favour the view that it is a degenerative change. Since it is difficult, perhaps unimportant, to decide as to its nature, it is perhaps best to describe it as a fatty change. As to the significance of the change, its presence accords with the recent observation that the cortex does not yield the active principle[47] of the suprarenal extract, and that relatively the suprarenal bodies are far more active in early life than afterwards.

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[46] *Archiv. Ital. de Biolog.*, xvii, p. 286.

After removal of one suprarenal body in young animals, Stilling[48] noticed that the remaining one hypertrophied; while so doing fat disappeared from the cortex for a time but returned after some weeks. Fatty change, though it may be a result of morbid processes elsewhere, cannot be said to give rise to any symptoms on its own account. It is interesting to note that while atrophy of these organs may be associated with symptoms of Addison's disease, fatty change has no such causal relation.

LARDACEOUS DISEASE.

When attacked by lardaceous disease the suprarenal capsules appear but slightly increased in size, and have a somewhat translucent appearance on section. On applying the iodine test the cortex becomes a dark brown, while the medulla remains of a grey or greyish yellow. The appearance thus presented is the reverse of that seen in health. The suprarenal bodies are among the organs which undergo the lardaceous change comparatively frequently. In fifteen cases of well-marked lardaceous disease I found the suprarenal capsules affected in eight; in three of the cases it was slight, so that microscopic examination was necessary to determine its presence.

According to Cornil and Ranvier[49] it is rare, and only attacks the vessels of the medulla. In my cases, however, it was always best marked in the vessels running vertically through the cortex; and, though it may be present in the medulla, it is always less marked there than in the cortex. Orth[50] describes the lardaceous change as occurring chiefly in the region of the zona fasciculata.

CYSTS.

Cysts in the suprarenal body are very rare; the occurrence of ecchinococcus may be mentioned,[51] and cysts the result of former hæmorrhages have been met with. I have seen a cyst the size of a cherry containing tenacious fluid. Virchow has suggested that cysts may be formed by a softening down of adenomata of the suprarenal capsules. In primary sarcomata of the suprarenal bodies cysts frequently occur.

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[47] Oliver and Schäfer, *Proc. Phys. Soc.*, March 1895.

[48] *Rev. de Méd.*, 1888, p. 460.

[49] Vol. ii, p. 549.

[50] *Spec. path. Anat.*, vol. ii, p. 14.

[51] St. Thomas's Hospital Museum, 1454.

TUBERCLE.

In general tuberculosis a few scattered miliary tubercles are occasionally seen in the cortex. In chronic tuberculosis the inflammatory process begins in the medulla. In the early stages, before caseation has occurred, the inflammatory granulation tissue has a firm speckled appearance, and microscopically contains numerous vessels. Caseation, softening, or calcareous infiltration, may all follow as in other tuberculous formations, but it is highly improbable that caseous material is ever absorbed or disappears. Tubercle is frequently found without any signs or symptoms having been present. In 1,050 *post-mortems* in which I have examined the condition of the suprarenal bodies, there were 131 cases in which death was directly or chiefly due to tuberculous disease, and in 18 of these cases there was caseation in the suprarenal capsules, without there being any evidence of Addison's disease. In 11 instances the caseation was unilateral, and in 7 bilateral.

In the decennial periods it is noteworthy that in the 23 cases in which death occurred under 10 years of age, no tubercle was found in the suprarenal bodies, while out of 17 cases in the period between 10 and 20 years of age caseation occurred twice on both sides and three times unilaterally. In the third period the proportion of caseous suprarenal bodies falls, but rises again in the 10 years between 30 and 40 to 6 out of 28; in 3 of these the lesion was bilateral.

There appears, therefore, to be immunity from tuberculous inflammation in the first few years of life in the case of the suprarenal bodies:

Years.........	1-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	Total.
Cases of tubercle...	23	17	29	29	17	10	5	1	131
No. of tuberculous suprarenals	0	5	2	6	1	2	2	0	18

SYPHILIS.

Gummata are occasionally found in the suprarenal bodies. I have seen one case in which there were multiple small gummata in the cortex. In one case of congenital syphilis kindly given me by Dr. J. W. Carr, I found a small gumma in the medulla of the suprarenal body.

ACTINOMYCOSIS.

Extension of an actinomycotic abscess from the right lobe of the liver into the right adrenal body has been recorded.[52]

SIMPLE TUMOURS.

Adenomata may be of two kinds, of which the first is much the commonest: (1) Multiple small yellowish nodules, situated on the cortex of the organ; they are not marked off by any capsule from the surrounding tissue, but differ from it in being the seat of very advanced fatty change. In other respects, the cells composing them are like the cells of the suprarenal cortex. They are sometimes mistaken for tubercles undergoing caseation; in this connection it is well to remember that chronic tuberculosis begins in the medulla. Virchow described adenomata of the medulla as gliomata, taking the view that the interstitial tissue of the medulla was akin to neuroglia. Manasse[53] has described giant cells in adenomata; I have never met with this appearance. (2) Large adenomata are almost always found singly in the suprarenal capsule, though they may be bilateral. They do not involve the whole of the organ, but form distinctly localised tumours, which may attain a very considerable size. They arise as a rule in the cortex, either from one or from more of its zones, and project usually from one side, though the whole thickness of the organ may be affected. They are a magnified edition of the small multiple suprarenal adenomata. Small ones may be present with them in same organ.

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[52] Kanthack, *Path. Trans.*, 1894, p. 238.

The cells contain a large amount of fat, and this accounts for the pale yellow colour of the adenomata. They may be distinguished from sarcomata by the absence of extravasation into their substance, and by their microscopic structure. Occasionally the fatty change is so advanced that they appear softened or necrosed. Commonly they have no more supporting fibrous tissue than the rest of the organ, but in other cases the quantity of fibrous tissue is much in excess, so that the term fibro-adenoma may be used. I have seen an example of this variety in which the cells did not show any fatty change, and in which hyaline degeneration of the vessels, which were numerous, was well marked.

Virchow described them under the name of struma lipomatosa suprarenalis; and recently from analogy they have been termed adrenal goîtres, though it must be regretted that a name of such purely local application as goître should be applied to a tumour in the abdomen.

Suprarenal "rests" taking on adenomatous growth in the kidney are, according to Horn,[54] responsible for some of the tumours which have been called adenoma of the kidney.

The existence of adenomata or hyperplastic tumours of the suprarenal bodies suggests the interesting speculation whether any symptoms can be correlated with this condition. Addison's disease and myxœdema have some analogies. Exophthalmic goître is apparently due to altered structure and secretion of the thyroid gland. Is there any disease analogous to Graves's disease connected with the adrenals? The absence of any symptoms in association with adenoma or hyperplasia of the suprarenal bodies may be due to the fact that they nearly always show extreme fatty change, and so cannot be functionally active. Schäfer and Oliver[55] have quite recently shown that the cortex does not yield the active principle of suprarenal extract; hence hyperplasia of the cortex would not lead to any modification of the suprarenal secretion. A specimen of ganglionated neuroma has been described.[56] Dr. Payne[57] has recorded a case of angeioma of the suprarenal capsule; there were similar growths in the ovaries and many in the liver.

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[53] *Virchow's Archiv*, Bd. 133, p. 391.

[54] *Virchow's Archiv*, cxxvi, p. 191.

[55] *Proc. Phys. Soc.*, March 16, 1895.

[56] *Virchow's Archiv*, lxxxv, p. 554, 1881, Weichselbaum.

[57] *Path. Trans.*, xx, p. 203, St. Mary's Hospital Museum, 1054.

Primary Malignant Growths.

Both carcinoma and sarcoma of the suprarenal capsules have been described, but generally the histological structure seems to be a vascular rather large-celled sarcoma. In some cases both organs have been the seat of primary malignant growths. The growth starting in the suprarenal body expands it, and may grow down the suprarenal vein or into the inferior vena cava.

By direct continuity the growth often invades the upper part of the kidney and, on the right side, the corresponding lobe of the liver. In some cases the growth may involve the pelvis of the kidney and give rise to hæmaturia. When the growth is extensive and invades the whole of the kidney, it is necessarily very difficult to say whether it began in the suprarenal or in the kidney. Secondary growths occur in the liver most frequently, but also in the lungs, kidneys, bones,[58] and skin.

Dr. Dickinson[59] mentions that in a case of sarcoma of the suprarenal body, the colon did not form an anterior relation of the tumour, as is the case in renal tumours; and since reading this I have seen two cases in which the tumour appeared above the colon, which was somewhat displaced downwards. The soft vascular growths have a tendency to necrose, and so to become excavated into hæmorrhagic cysts; a specimen of a cystic sarcoma as large as a cricket ball is in the London Hospital Museum.

In young children excessive development of hair and of the genital organs has been noted in connection with suprarenal sarcoma. In 1,050 *post-mortem* examinations there were three cases of primary malignant growth in the suprarenal capsules. In two cases the growth was a sarcoma; in one the cells were large and round, the other was spindle-celled; the round-celled growth was extremely vascular. The third case was a spheroidal-celled carcinoma.

H. Morris and Sutton speak of tumours of the suprarenal bodies which give rise to secondary growths as being analogous to those rare and interesting cases of bronchocele,[60] which produce secondary growths in bone and elsewhere. Morris[61] described the growth in one of these cases as being composed of tissue like that on the medulla of the suprarenal body. It seems difficult to distinguish between such a tumour and a vascular large round-celled sarcoma.

Sutton[62] described an adenoma of the suprarenal body in a marmot giving rise to numerous secondary nodules on the liver, which on section presented a curious mottled appearance, and also to a single nodule in the spleen. Histologically the growth resembled suprarenal cortex, and was therefore not considered malignant. Abnormally low bodily temperature has been noticed in primary suprarenal sarcoma,[63] but the temperature in a rapidly growing sarcoma from the right suprarenal body[64] in a coloured girl aged 8 was on an average 100°.

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[58] *Vide* Case of Infant 9 Months Old, recorded by Cohn (British Medical Journal Epitome, May 19th, 1894).

[59] *On Renal and Urinary Affections*, vol. iii, p. 722.

[60] Described by H. Morris, *Path Trans.*, xxxi; W. Haward, *ib.*, xxxiii.

[61] British Medical Journal, January 1st, 1893.

[62] *Journal of Anat. and Phys*, vol. xix, p. 415.

[63] *Wiener med. Woch.*, Nos. 11-12, 1889.

[64] Roberts, *Internat. Clinic.*, Series iii, vol. i, p. 203.

Examples of renal sarcoma arising in suprarenal "rests" have been described. Not only is their structure much like that of primary suprarenal sarcoma, but they show a similar tendency to the formation of hæmorrhagic cysts and to undergo necrosis. Lubarsch[65] has found glycogen in eight cases, and regards this as indicating their embryonic origin. Schmorl[66] suggests that some of the primary neoplasms of the liver may similarly be due to proliferating changes in a suprarenal "rest." Such a theory would explain some aberrant sarcomata, apparently primary, in the liver, such as one I have lately seen with hæmorrhagic cysts inside it.

SECONDARY GROWTHS IN THE SUPRARENAL BODIES.

In 1,050 *post-mortem* examinations carcinoma of various parts of the body occurred 63 times, and in 7 of these the suprarenal bodies contained secondary growths.

There were 24 cases of sarcoma, and of these only 2 cases showed metastatic growths in the suprarenal bodies. The occasional association of primary sarcoma[67] at the root of the lung and secondary growths in the suprarenal bodies is possibly explained by there being a connection through the thoracic duct.

Norman Moore,[68] in 123 cases of new growth (102 carcinoma, 21 sarcoma) found secondary growths in the suprarenal bodies in 8. Three of these were carcinoma, 3 sarcoma, and 2 are described as endothelioma, the primary growth being in both cases in the heart.

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[65] *Virchow's Arch.*, cxxxv, p. 149.

[66] *Beitr. Ziegler.*, vol vi, 1889, p. 528.

[67] Hale White and F. C Turner, *Path. Trans.*, xxxvi.

[68] *Medical Pathology*, p. 355.

LECTURE II.

PHYSIOLOGY OF THE SUPRARENAL BODIES.

OF the suprarenal capsules it may be said that there can be no satisfactory pathology until their physiology is known. Addison himself expressed no more definite view than that the suprarenal bodies minister in some way to the elaboration of the blood, and that the interruption of their functional activity, caused by their destruction, was responsible for the symptoms described by him. Brown-Séquard, stimulated by the pathological researches of Addison, investigated the physiology of the suprarenal capsules in dogs, cats, rabbits, and guinea-pigs, by removing them and noting the results. From a series of sixty experiments on animals he came to the following conclusions:

1. That the suprarenal capsules are absolutely essential to life.
2. That suppression of their functions is more rapidly fatal than suppression of the secretion of urine. When both suprarenal bodies were removed the animal lived about eleven hours; when one only was removed the animal died after seventeen hours.
3. That the function of the suprarenal bodies was to modify or to destroy a substance which had the property of transforming itself into pigment. When the suprarenal capsules are removed or destroyed the pigment collects in the blood, but there is no pigmentation of the skin.
4. That in an animal from whom the suprarenal capsules have been removed the blood becomes poisonous, and when injected into other animals of the same species often produces death.

Dominicis[1] quite recently has found removal of the suprarenal capsules invariably fatal in a very few hours. Gratiolet[2] repeated Brown-Séquard's experiments; he often removed the left suprarenal capsule in guinea-pigs without any serious symptoms resulting, but the additional removal of the right one was fatal in three days, and since peritonitis and hepatitis were present, the fatal result was thus explained by him.

Philippeaux[3] removed both the suprarenal capsules from rats without producing any symptoms, and therefore considered that death, when it follows this experiment, is due to lesions of other organs. Tizzoni[4] criticises these results, and considers that a sufficient time was not allowed to elapse after the operation, and that because the animals did not die soon after the removal of the suprarenal capsules it was too hurriedly assumed that they had recovered.

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[1] *Archiv. de Phys.*, 1894.

[2] *Compt. Rend.*, tome xliv.

[3] *Compt. Rend.*, tome xliv.

[4] *Ziegler's Beiträge*, 1889, p. 6.

George Harley[5] came to the conclusion that the suprarenals are not absolutely necessary to life; that when death follows their removal it is in most cases due to injury to neighbouring tissues, chiefly the sympathetic, and that from the closer relation in the animals experimented on of the right suprarenal to the semilunar ganglion that the removal of the right suprarenal is more likely to lead to a fatal termination than that of the left. He successfully removed both suprarenals from rats which survived the operation without ill effects for months.[6]

Schiff, Nothnagel,[7] Martin-Magron, Chatelain,[8] and recently Pal[9] and Berdach,[10] obtained results in favour of the view that the suprarenal bodies were not necessary to life. In a later paper Brown-Séquard expressed himself as convinced of the correctness of his views, and further stated that the results of removal could not be explained by any concomitant lesions such as peritonitis, hepatitis, damage to kidneys, renal veins, inferior vena cava or sympathetic.

In addition to Tizzoni's criticism that the animals operated on were not kept under observation sufficiently long, and that when they died, two or three months after removal of the suprarenal, their death was ascribed to accidental causes, while in reality it might have been due to the effects of the operation, there is a further and quite justifiable objection to negative results of experimental ablation of the suprarenal bodies. This objection is that even when both suprarenal bodies have been completely removed the presence of accessory suprarenal bodies in various situations mentioned above may compensate for the removal of the normal glands. Stilling has shown that under such conditions the accessory adrenals may undergo a compensatory hypertrophy. The *rôle* thus played by accessory suprarenal bodies is analogous to that played by accessory thyroid glands on removal of the whole of the thyroid gland either for goître or experimentally. Alexander points out that, owing to the very close connection of the right suprarenal capsule with the inferior vena cava it is not improbable that fragments of it might be left behind, and by compensatory hypertrophy might prevent the development of symptoms due to complete removal.

Though far from being unanimous, the majority of investigators inclined towards the view that the function of the suprarenal bodies was unknown or, at least, unimportant. At the same time the opinion was gradually gaining ground that the symptoms of Addison's disease were not due so much to destruction of the suprarenal capsules as to irritation of the sympathetic trunks and ganglia around them. Probably as a result of the nervous theory of Addison's disease, expressed, among others, by Dr. Greenhow,[11] the subject of the function of the suprarenal capsules became for a time neglected.

MacMunn,[12] by means of spectroscopic examination, found a histohæmatin in the cortex and free hæmochromogen in the medulla of the suprarenal capsules. Hæmochromogen,

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[5] *British and Foreign Medico-Chirurgical Review*, 1858, vol. xxi, p. 204.

[6] *Vide* University College Museum, 3415.

[7] *Zeit. f. klin. Med.*, 1880.

[8] Quoted by Brault, *Traité de Méd.*, vol. v, p. 891.

[9] *Sem. Méd.* November 3rd, 1894.

[10] *Wiener med. Woch.*, No. 31, 1894.

[11] Croonian Lectures, p. 68.

[12] *Phil. Trans.*, 1886, part i; BRITISH MEDICAL JOURNAL, February 4th, 1888.

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the writer considers, is an excretory stage in the history of of blood pigment, and is probably formed by a downward metabolism from hæmoglobin and histohæmatins. He put forward the hypothesis that the function of the suprarenals is to pick out of the circulation the effete or worn-out pigments of the blood and their accompanying proteids. He further stated that when these pigment-metabolising organs are diseased there should be present in the urine incompletely metabolised pigments. This he found in a body he called urohæmatoporphyrin.

Foà and Pellacani[13] found injection of aqueous and alcoholic extracts of suprarenal bodies fatal to frogs, rabbits, and dogs. Alexander[14] believed that in the preparation of these extracts artificial poisons were produced. Schäfer and Oliver[15], by injection of large quantities (equal to 50 grains of the gland) of aqueous suprarenal extract, produced death in rabbits in twenty-four hours.

The poisonous body has been thought to be neurine, which, being continually formed by the activity of the muscular and nervous systems, is eliminated or destroyed by the suprarenal bodies (Marino Zucco,[16] Carbone[17]); it is said to have been found in urine of Addison's disease.[18]

It was suggested that the toxic effects were due not so much to neurine as to combinations of phosphoric acids with that base (Marino Zucco[19]), the toxic properties of the extract being destroyed by the addition of hydrochloric acid, which broke up the phosphate of neurine.

Oliver and Schäfer showed that the symptoms of toxic doses of suprarenal extract do not correspond to those of neurine, and that the phosphate and hydrochlorate of neurine have the same effect as the base. Supino[20] repeated Marino Zucco's experiments with a negative result as regards neurine.

What the active principle of the extract of the suprarenal bodies may be is at present not established. Bodies such as leucin (Virchow), lecithin,[21] taurocholic and hippuric acid (Vulpian and Closz), and benzoic acid have been extracted from the suprarenal capsules, but there is nothing to show that the effects of injection of suprarenal juice are due to any of them, or that they have been picked out of the circulation, and are in process of being removed by the instrumentality of the suprarenal bodies.

Mr. Moore[22] has found that the active principle of suprarenal extract is not a proteid or a carbohydrate. It is not affected by acids or by boiling for some minutes, but is destroyed by alkalies, reducing agents, and by continued boiling. It dialyses and it has a powerful reducing action. It has not been isolated; its properties resemble those of a reducing agent found in 1856 by Vulpian in the medulla of the suprarenal bodies.

As leucin is a product of downward metabolism of proteids, its occurrence in extracts of the suprarenal bodies is probably explained as the result of decomposition taking place. Leucin is not poisonous. Subcutaneous injections of increasing quantities of leucin into animals have been described as giving rise to nephritis[23] and albuminuria. These results do not follow removal of the suprarenal bodies or the injection of suprarenal extract, and since leucin is normally transformed by the liver into urea, there is no reason to believe that leucin has anything to do with the suprarenal bodies.

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[13] *Archiv. della Scienz. Med.*, vol. vii, fascic. ii, 1883.

[14] *Ziegler's Beiträge*, xi, vol. No. 8.

[15] *Proc. Phys. Soc.* March 10th, 1894.

[16] *Ziegler's Centralblatt*, vol. iii, No. 24; *Archiv Ital. de Biolog.*, Tom. x, fascic. iii, p. 325.

[17] *Ziegler's Centralblatt*, vol. v, No. 10.

[18] Marino Zucco et Dutto, *Bollettino della R. Accad. Med. di Roma.*

[19] *Loc. cit.*

[20] *Riforma Med.*, 1892; *Ziegler's Centralblatt*, 1892.

[21] Alexander, *Ziegler's Beiträge*, vol. xi.

[22] *Proc. Phys. Soc.*, March 16th, 1895.

Lecithin is found in most parts of the body; in itself it has no toxic effects, but it may be changed into choline,[24] which has poisonous properties like those of neurine. The effects of neurine and of extract of suprarenal capsules have been shown by Schäfer and Oliver to be different; hence as the properties of neurine and choline are alike,[25] it may be concluded that the presence of choline or lecithin cannot explain the activity of suprarenal extract, or an accumulation of these bodies in the blood account for the toxic symptoms resulting after removal of the suprarenal capsules.

In the same way benzoic, hippuric, and taurocholic acids cannot be held to be responsible for the active properties of suprarenal extract, or, on the hypothesis that they accumulate in the body on removal of the capsules, for a toxic condition of the blood.

Tizzoni,[26] in experimental removal of the suprarenal capsules in rabbits, obtained remarkable results, which are the same whether one or both organs are removed or whether one is first removed and later the other. It makes no difference if the crushed suprarenal capsule is left to be absorbed in the body. Leaving the crushed suprarenal capsule in the body does not lead to any symptoms of auto-intoxication, as might have been expected if the suprarenal capsules excreted any poison from the body.

Death occurs either shortly after the operation or after a long interval—130 to 997 days—the symptoms being much alike in either case, but after the prolonged interval the symptoms resembled those of Addison's disease more than in the former case. It is interesting to compare these results with the acute and chronic myxœdema[27] produced by experimental thyroidectomy in monkeys. Tizzoni says that the function of the suprarenal bodies is not taken on by any other organ, as was suggested by Brown-Séquard—a hypothesis which Philippeaux had previously impugned by removing in the same animal the thyroid, spleen, and suprarenal bodies without fatal results.

In animals which died soon after the removal of one or both suprarenal bodies a progressive emaciation, with no definite cause to account for it, was noted; death came comparatively suddenly, being preceded by depression, lowered temperature, and convulsions. On the other hand, in animals who died at a time remote from the operation their condition remained normal for a considerable period; some time before death loss of weight was noticed. Pigmentation came on slowly, first around the mouth and nostrils, then on the oral mucous membrane and on the tongue.

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[23] Gaucher, *Rev. de Méd.*, 1888, p. 883.

[24] Halliburton, *Chemical Physiology and Pathology*, p. 529.

[25] Halliburton, p. 530.

[26] *Ziegler's Beiträge*, vol. vi, No. 1, 1889.

[27] Clin. Soc. Report on Myxœdema, p. 80.

Pigmentation occurred in 13 out of 30 rabbits dying at a period remote from the operation, whereas Nothnagel found it in only 3 out of 153 cases in which the suprarenal bodies were crushed. Death was ushered in by diminution of motor power and blunting of sensation, coma, convulsions, and opisthotonos.

The changes in the nervous system were occasionally visible to the naked eye, but though microscopic changes were present in the majority of cases they were by no means universal.

In cases which died soon after operation, disturbance of the circulation, congestion, and hæmorrhages were seen in the grey matter of the cord, especially around the central canal and also in the medulla, where hæmorrhage about the vagus nucleus accounted for death. The change was more intense in the cervical and upper dorsal regions than in the lumbar part of the cord. The pia mater was inflamed, and the grey matter of the cerebrum and the lining of the lateral ventricles underwent a similar, though more diffuse, change to that in the grey matter of the cord. In animals dying long after the operation the parts of the cord affected were the same, and showed inflammatory exudation with atrophic changes of the nerve elements, while in addition a systemic degeneration may be seen in Goll's columns. Degenerative changes occur irregularly in the peripheral nerves. In connection with the situation of these changes which tend to descend towards the suprarenal bodies, it should be noted that Arnaud and Alexais[28] have observed, after removal of the suprarenal bodies, an ascending degeneration, starting from the region of the suprarenal bodies, through the semilunar ganglia to the lateral region of the cord.

Tizzoni argues that as the same result follows removal whether of one or of both organs the cause cannot be a toxic agent, and sees nothing to support the theory that it is due to changes or any trophic influences exerted by the adrenal bodies on the central nervous system. He considers that the nervous lesions are due to alterations in the circulation through the blood vessels, due to influences travelling in the sympathetic, and primarily due to the destruction of the suprarenal bodies. However, he finds that changes in the solar plexus and semilunar ganglia are not always present. He suggests that in cases of some standing, where no change is found, degenerative changes did occur but have now passed away. He, however, leaves the connection between removal of the suprarenal bodies and the nervous lesions open. The fact that death sometimes occurs soon, at other times after a prolonged interval from the operation, he believes is due to the varying amount of damage done in the process of ablation. He concludes by considering the suprarenal bodies of importance from their close relation to the sympathetic, and does not regard them as functional glands.

Stilling[29] thinks that Tizzoni's plan of removing the suprarenal bodies from the back may cause the changes in the central nervous system by a direct extension of the inflammatory process from the wound to the cord. Stilling reached the suprarenal bodies by laparotomy, and though he examined for changes in the central nervous system, never

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[28] Quoted by Boinet, *Sem. Méd.*, November 3rd, 1894. The original pape appears to be in *Marseille Méd.*, 1891, xxviii.

[29] *Rev. de Méd.*, 1890, p. 830.

[illegible]

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[illegible]

[illegible]

[illegible]

[illegible]

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[1] [illegible]

[2] [illegible]

[3] [illegible]

[4] [illegible]

removed into healthy animals, and this killed the animals; but it appears probable that they died from ordinary septicæmia.

In addition to Boinet's work the observations of Thiroloix[35] show that the results of ablations are to be explained by interference with the functional activity of the suprarenal bodies, and not by the mere traumatic effect of their removal. Removal of one suprarenal body in dogs was followed by hypertrophy of the other and by no symptoms; subsequent removal of the remaining organ led to coma and death. It is very improbable that this was due to injury to the sympathetic, because if the remaining organ was separated from all its nervous connections and left *in situ* no symptoms resulted. The last procedure would entail fully as much, if not more, damage to the sympathetic as removal of the organ.

In the history of all important ablation experiments, for example, the thyroid, pancreas, and kidney, the typical symptoms and physiological changes have been explained by some observers as due rather to secondary effects on the surrounding nerves than to the specific effect of removal of the gland. Thus Munk believed the cachexia strumipriva was a result of damage to the vagus and sympathetic; from Horsley and G. R. Murray's work there is now no doubt that the important factor is the absence of the secretion of the gland.

With regard to the pancreas, Minkowski separated the pancreas from all its nervous connections without giving rise to diabetes mellitus, while Rose Bradford showed that the sympathetic played no part in the phenomena he obtained in extirpation of the kidney.

G. Oliver and Schäfer,[36] working with suprarenal extracts (watery, glycerinic, or alcoholic) of man, calves, sheep, and dogs, and injecting them into dogs, cats, rabbits, and frogs, have found:

1. A rise of blood pressure due to arterial constriction. This is best seen after section of the vagi, which prevents the concomitant inhibition of the heart. The blood pressure may rise to double or even quadruple the normal and is not affected by stimulation of the depressor nerve. In a limb the constriction of the vessels may be shown by the diminution in bulk, as measured by the plethysmograph, or in the kidney, by Roy's oncometer. As this effect remains after section of the cord or of the nerves going to the limb it is due to peripheral and not to central influences. The arteries are so firmly constricted as to suggest the use of suprarenal extract as a hæmostatic agent in hæmophilia, purpura, etc.

2. On the heart suprarenal extract exerts a marked inhibitory effect through the vagus; the beats become feeble and slow. On cutting the vagi the heart beats much more quickly than normally, and its force is much augmented.

3. After a hypodermic injection of extract (equal to 1 or 2 grains of the gland) a frog shows absence of knee-jerks, and appears paralysed. The muscles react to direct stimulation or to stimulation of their nerves, but the contractions are modified, the relaxation period being greatly prolonged,

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[35] Anatomical Soc., Paris, February 2nd, 1894.

[36] *Proc. Phys. Society*, March 10th, 1894; March 16th, 1895; Schäfer, Address in Physiology, British Association, 1894; G. Oliver, *Pulse Gauging*, p. 86-90.

as in veratria poisoning. The effect is not at all comparable to that produced by curare. The effects come on thirty seconds after intravenous injection, and do not pass off so rapidly as the cardio-vascular phenomena; hence it appears that the extract becomes stored up in the muscles.

4. The active principle of the extract is present only in the medulla and not at all in the cortex.

Suprarenal extract acts on the arteries in exactly the opposite way to thyroid extract. Schäfer[37] does not commit himself as to whether the extract contains a useful substance, secreted by the suprarenal bodies, to be subsequently used in the economy, or whether the extract contains a poison which is formed by the tissues during their activity and is carried by the blood to be rendered innocuous by the adrenal bodies. But from the encouraging results he obtained in the treatment of Addison's disease it appears that Dr Oliver[38] probably regards it as a useful internal secretion.

Three deductions are possible from these researches into the physiology of the suprarenal bodies:

1. That they have no proper function, and are important only from their close relation to the sympathetic.
2. That they are excretory glands, removing pigment and toxins from the circulation.
3. That they are secretory glands, providing an internal secretion which is of use in the economy.

With the exception of Tizzoni's results, all modern work points strongly to the conclusion that the suprarenal capsules are functional, and that their importance does not depend on their anatomical relation to the sympathetic. The presence of accessory adrenal bodies or incomplete removal have been shown to be possible explanations of the negative results obtained by some of the earlier investigators.

The evidence is sufficiently strong to warrant the conclusion that the adrenal bodies are functional glands. It is, however, more convenient to postpone any discussion as to whether that function is of the nature of an excretion or a secretion until the explanation of Addison's disease is dealt with, since the physiology and pathology of these organs are so inextricably blended. It is interesting that the thyroid gland was first considered as vaguely hæmatopoietic, or as having no function at all, then as an excretory gland removing mucin from the economy, while now it is firmly established as an anabolic gland providing an internal secretion.

CONDITION OF SUPRARENAL CAPSULES IN ADDISON'S DISEASE.

In Addison's original paper (published in 1854) 11 cases are recorded; 5 of these cases had caseous tubercle in both suprarenals, and in 1 case tubercle was present in one suprarenal. One case (No. 4) appears to have been an example of cirrhosis and atrophy. In 3 cases there were secondary carcinomatous growths in the suprarenals, bilateral in 1 case, and unilateral in the other 2. In 1 additional case there was a secondary nodule of carcinoma blocking the right suprarenal vein associated with hæmorrhage into the corresponding capsule, but without any growths in either.

Addison took a characteristically broad view of the relation of the symptoms to the morbid lesions, and expressed himself to the effect that any morbid lesion of the suprarenals might produce the same result, and that the result depended not so much on the nature of the organic change as upon the interruption of some special function of those organs. While the discovery was Addison's, the general recognition of this disease is, perhaps, chiefly due to the vigorous and loyal efforts of Dr. Wilks.

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[37] Address in Physiology, p. 8.

[38] G. Oliver, *Pulse Gauging*, p. 89.

After the publication of his original memoir, Addison appears to have been inclined to modify his views as to a multiplicity of morbid conditions of the suprarenal capsules giving rise to the same series of symptoms, and to have wished to have removed from among the cases in his monograph those of carcinoma of the suprarenal capsules. While, with regard to the cause of the symptoms, he conjectured that the intimate connection of the suprarenal bodies with the sympathetic had a large share in the production of the symptoms, thus in some degree throwing over his expressed opinion that the interruption of some special function of the suprarenal capsules was the explanation of the characteristic symptoms.

According to Dr. Wilks,[39] Addison, on the first occasion of bringing the discovery before the profession at a meeting of the now extinct South London Medical Society in 1849 suggested the nerve theory in the following words: "We know that these organs (the suprarenals) are situated in the immediate vicinity and in contact with the solar plexus and semilunar ganglia, and receive from them a large supply of nerves, and who can tell what influence the contact of these diseased organs might have on these great nerve centres, and what share that secondary effect might have on the general health and in the production of the symptoms presented?"[40]

According to Dr. Wilks all genuine cases of Addison's are due to one and the same lesion of the suprarenal capsules. This view might be called the unity of Addison's disease. This lesion could now be considered to be tuberculous, but Dr. Wilks considered it to be a primary inflammation[39] comparable to hepatic cirrhosis, and regarded the atrophied cirrhotic condition of adrenal bodies sometimes seen as the last stage of the fibro-caseous change.

Dr. Greenhow[41] was a follower of the view of the unity of Addison's disease, and therefore criticised severely all the recorded cases in which the morbid condition of the suprarenal bodies was other than the fibro-caseous change, and concluded either that the symptoms (especially the pigmentation) were not characteristic of Addison's disease, or that the lesion found was incorrectly described.

The fibro-caseous change begins first in the medulla, and spreads gradually throughout the whole of the organ, and after destroying the cortex may set up inflammation in the adjacent tissues and adhesions to neighbouring organs. The semilunar ganglia and solar plexus are often described as being invaded by the inflammatory process, and again have been found quite free from any morbid change. Typically this lesion is bilateral, but cases of well marked Addison's disease occur with a unilateral lesion.[42]

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[39] *Pathological Anatomy*, p. 509, 1889.

[40] The paper is briefly reported in the *London Medical Gazette* (new series), vol. viii, 1849, p. 517.

[41] Croonian Lectures, 1875.

[42] Addison's *Memoir*, p. 37. Greenhow, p. 67. Bedford Fenwick, *Path. Trans.*, vol. xxxiii.

The caseous change has very frequently been shown to contain bacilli, though in others repeated examinations have failed to demonstrate their presence. I am indebted to Professor Delépine's kindness for leave to mention such a case of Addison's disease with caseous suprarenal bodies in which no tubercle bacilli could be found. Subcutaneous inoculation of caseous material into guinea-pigs after Villemin's method[43] did not lead to tuberculosis. So that although the lesion is generally tuberculous, it is not necessarily so in all cases. This condition is certainly the one more commonly found in association with Addison's disease. In 285 cases (collected by Lewin) of the disease this lesion was present in 211. Tuberculous inflammation of the suprarenal bodies, like that of the lungs, is much commoner than any other form of chronic inflammation. It is interesting to contrast the liability of the suprarenal bodies to tubercle with the marked immunity of the thyroid gland.

The late Dr. Habershon[44] first showed that as the result of inflammation spreading from the suprarenal bodies the semilunar ganglia and their branches may become surrounded by dense fibrous tissue. Sclerosis of the abdominal sympathetic has been confirmed in cases of Addison's disease by many observers.

Dr. Greenhow[45] described two stages in the process: (1) a stage of irritation of the semilunar ganglia and the nerves connecting them with the suprarenal capsules, as shown by redness and swelling; and (2) a further stage of atrophy and fatty degeneration.

On the other hand, the absence of any alteration of these same structures has been repeatedly recorded. The extremely careful examinations made by Dr. Robinson for Dr. Mann[46] on two cases of Addison's disease serve as a model for such investigations, since a control examination was made at the same time of the same structures from a patient of the same age where there was no reason to suspect anything abnormal.

Von Kahlden[47] criticises the published observations as to the condition of the semilunar ganglia and sympathetic in cases of Addison's disease, and does not consider either the positive or negative results of much value.

He examined two cases of Addison's disease, and found[4] the following changes in the semilunar ganglia: Hyaline degeneration and thickening of the vessel walls, small cell infiltration, and hæmorrhages in connection with their adventitia, and pigmentary atrophy of the ganglion cells and thickening of their capsules. He considers that these changes have a direct causal relation to the symptoms of Addison's disease. He found the splanchnic nerves in the two cases quite healthy. Jurgens, however, has described degeneration of the splanchnics in Addison's disease. The bearing of these observations must be considered in the light of Hale White's[49] description of the normal histology of the semilunar ganglia in adults. The cells are pigmented and atrophied, the degree of atrophy increasing with age; the fibrous tissue was often very much increased in amount, and in a few instances the section was crowded with leucocytes without any apparent reason. No constant arrangement in small blood vessels could be discovered. These changes occurring normally have such a close resemblance to those to which von Kahlden attaches importance as being responsible for the symptoms of Addison's disease that it seems very doubtful whether the changes described by this observer had anything to do with the production of the symptoms of Addison's disease.

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[43] Delépine, BRITISH MEDICAL JOURNAL, September 23rd, 1893.

[44] *Guy's Hospital Reports*, 1864.

[45] Royal College of Physicians, Croonian Lecture, 1875, p. 73.

[46] *Lancet*, i, 1891, p. 652.

[47] *Virchow's Archiv*, cxiv, 1888, p. 91 to 93.

[48] *Loc. cit.*

[49] *Journal of Physiology*, vol. x, 1889, p. 345.

Malignant disease of the suprarenal capsules occasionally gives rise to some of the symptoms of Addison's disease, such as gastric disturbance, extreme debility, and pigmentation. Typical cases of Addison's disease are naturally those in which there is no other organ affected, and in which the disease runs its own course without any complications. When growths develop secondarily in the suprarenal bodies the primary growth may give rise to symptoms which throw into the shade or obscure any that may be due to interference with the suprarenal bodies. The comparatively rapid progress of the primary malignant disease may kill the patient before the secondary affection of the suprarenal bodies has had time to lead to any distinct symptoms.

Again, in many cases the presence of malignant disease, if ascertained, would be quite sufficient to explain any symptoms which otherwise might be due to suprarenal disease.

Still, from Addison's time downwards examples of secondary malignant growths in the suprarenal capsules being associated with the symptoms, especially the pigmentation, of Addison's disease have been recorded, and it is, therefore, to be borne in mind that new growth in the suprarenal bodies may produce symptoms comparable to those met with in typical cases of Addison's disease.

It is undoubtedly true that the suprarenal bodies may be apparently almost completely destroyed by carcinoma, and yet no special symptoms result. The same, however, is true of tubercle, and especially where there is extensive tuberculous disease elsewhere. Perhaps in both cases death has occurred before symptoms characteristic of Addison's disease have had time to develop.

In primary malignant disease of the suprarenal bodies there seems little evidence that the symptoms of Addison's disease occur.

Well-established examples of simple atrophy[50] of the suprarenal capsules, without any fibrous increase in the substance of the organ, or of any fibrous adhesions around them, have often been described as giving rise to the typical clinical picture of Addison's disease. The atrophy in some of the cases was extreme, the organs in many cases requiring very careful and minute dissection. In some instances they are described as being of the size of peas. It cannot be wondered at that in some cases, as in Dr. Spender's, they are described as being absent. These cases are of great importance, as will be seen later, in supporting the view that the symptoms of the disease are due to the absence of the functional activity of the organs, and not to irritation of the neighbouring important sympathetic nerves. In these cases of atrophy the sympathetic plexuses and semilunar ganglia were in most instances carefully examined, and stated to be normal. The subject of atrophy of the suprarenal bodies has already been referred to.

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[50] Spender, BRITISH MEDICAL JOURNAL, 1858, p. 768. Marbais, *Berlin. klin. Woch.*, 1869, p. 481. W. Legge, *St. Bartholomew's Hospital Reports*, vol. x, 1874. Goodhart (2 cases), *Path. Trans.*, 1882, pp. 340 and 346. Davy, *Path. Trans.*, 1882, p. 360. Hebb, *Lancet*, vol. i, p. 9, 1883. Coupland, *Path. Trans.*, 1885, p. 423. T. Barlow, *Path. Trans.*. 1885, p. 433. Roloff (9 cases), *Ziegler's Beiträge*, 1891, Bd. ix. s. 329. Westminster Hospital Museum, Series xl, 785.

Chronic interstitial inflammation[51] of the suprarenal bodies, leading to atrophy, and homologous with atrophic cirrhosis of the liver, has given rise to typical Addison's disease. The chronic fibrosis is quite unconnected with the production of any caseous material, and does not show any evidence of tubercle, such as bacilli. The late Dr. Haddon compared this change in the suprarenal bodies to those met with in the thyroid gland in myxœdema, and expressed his opinion that the essential factor in Addison's disease is, as in myxœdema, a destructive change, the anatomical condition being of no consequence as long as it is destructive.

A few cases[52] showing an apparent connection between hæmorrhages into the suprarenals and blood cysts occupying them, on the one hand, and the symptoms of Addison's disease, on the other, have been recorded. Apart from disease of the suprarenals of the various kinds already mentioned, there are some cases recorded of symptoms like those met with in Addison's disease being associated only with alteration of the semilunar ganglia or abdominal sympathetic.

Guay[53] records two such cases: (1) Under the care of M. Raymond, of lymphadenoma. with some of the symptoms of Addison's disease the semilunar ganglia and solar plexus where found enclosed in masses of growth, but the suprarenal capsules were intact. (2) Under the care of Dr. Brault, a man with advanced phthisis, who was in the last stage of debility and markedly pigmented. The suprarenal bodies appeared normal to the naked eye, though microscopically there was a little chronic inflammation in the right one. In the right semilunar ganglion there was a small caseous nodule.

Dr. J. K. Fowler[54] has recorded a case under the care of the late Sir George Paget, in which the suprarenal capsules were healthy, but the semilunar ganglia and solar plexus were buried in a mass of lymphadenomatous growth. Clinically the case had marked pigmentation.

Von Kahlden[55] quotes a similar case recorded by Niesykowski in the *Gazette des Hôpitaux*, 1867.

To summarise the conditions of the suprarenal bodies recorded in cases of Addison's disease, there are the following:

1. The fibro-caseous lesion due to tuberculosis—far the commonest condition found.
2. Simple atrophy.
3. Chronic interstitial inflammation leading to atrophy.
4. Malignant disease invading the capsules, including Addison's case of a malignant nodule compressing the suprarenal vein.
5. Blood extravasated into the suprarenal bodies.
6. No lesion of the suprarenal bodies themselves, but pressure or inflammation involving the semilunar ganglia.

The first is the only common cause of Addison's disease. The others with the exception of simple atrophy may be considered as very rare.

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[51] Haddon, *Path. Trans.*, 1885, p. 436. (No adhesions to sympathetic); S. Martin, *Illustrated Medical News*, December 15th, 1888.

[52] Carrington, *Path. Trans.*, 1888, p. 454; also Gerhardt, *Medical Week*, November, 1893, p. 578.

[53] *Thèse pour le Doctorat* (Paris, 1873), p. 23, 32.

[54] *Lancet*, 1879, vol. i, p. 258.

[55] *Virchow's Archiv*, c. xiv.

ANATOMICAL DISTRIBUTION OF CUTANEOUS PIGMENT IN ADDISON'S DISEASE.

The pigmentation is an exaggeration of the normal, and is met with therefore on the face, neck, hands, anterior folds of axilla, nipples, perineum, and genitals. The occurrence of small pigmented spots on the skin is, according to Dr. Greenhow, characteristic. Any cause of irritation, such as pressure, the application of blisters, or inflammation of the skin, is followed by marked pigmentation. During the progress of the disease the hair has been noticed to become darker. Microscopically the pigment is found in the cells of the stratum Malpighii, the more superficial layers of the epidermis being quite or almost free from any pigment.

The dermis shows a few pigmented cells, "carrier cells," which it is thought convey the pigment from the blood vessels of the dermis to the stratum Malpighii. These wandering cells are found around the vessels in the superficial parts of the dermis, where they absorb pigment from the blood vessels,[56] the method of absorption being doubtful. That hæmoglobin is not absorbed directly is shown by the absence of iron from melanin, so that if the melanin in normal and abnormal pigmentation of the skin is eventually derived from the blood considerable metabolism must intervene.

Demiéville and Riehl[57] have found that the vessels of the cutis in the pigmented areas show small cell-infiltration and small hæmorrhages in their adventitia, and conclude that the extravasated blood pigment passes up to the cells of the stratum Malpighii, not in a soluble form as a chromogen, but as pigment particles, and thus accounts for the pigmentation of the skin.

Von Kahlden believes that the pigment of the stratum Malpighii is derived by means of carrier cells from the blood, but does not consider that disease of changes in the vessel wall or hæmorrhages around the vessels have any causal connection with pigmentation.

Nothnagel regards the exaggeration of the normal pigmentation met with in Addison's disease as due to functional, not organic, change in the vessel wall allowing increased transference of pigment to the stratum Malpighii.[58]

The general consensus of opinion is that the melanin of the stratum Malpighii is ultimately derived from the hæmoglobin, and that in abnormal pigmentation this process is exaggerated. Delépine,[59] however, has put forward the view that by the activity of the cell protoplasm of the stratum mucosum the melanin is manufactured, and passing out of the cells into the lymphatics of the corium, is carried away and tranformed into hæmoglobin. On the view that melanin is an antecedent and not a derivative of hæmoglobin, the carrier cells might be regarded as transferring the melanin from the epidermis to the lymphatics and vessels of the dermis. Averbeck and Burger[60] believe that the pigment in Addison's disease is due to very active metabolism in the cells of the stratum Malpighii.

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[56] Dixon Mann, *Lancet*, April 4th, 1891.

[57] Quoted by von Kahlden, *Virchow's Archiv*, cxiv, Bd. iv, p. 102.

[58] *Loc. cit.*, p. 112.

[59] *Proc. Phys. Soc.*, December 13th, 1890.

[60] Quoted by von Kahlden, *Virchow's Archiv*, cxiv, p. 97.

PIGMENTATION OF MUCOUS MEMBRANE.

Pigmentation of mucous surfaces is rarer, occurs in more advanced cases, and is usually regarded as being a sign of more value than cutaneous pigmentation. It may be found along the line of contact of the lips, on the cheeks, gums, or tongue, especially if there be any cause of irritation, such as a carious tooth. It is said to occur in the vagina[61]. The conjunctivæ[62] may in some cases, though very rarely, be pigmented.

Situation of the Pigment on the Mucous Membrane.—According to Dr. Greenhow[63] the pigment in the tongue is found in the same layer as in the skin, namely, the stratum Malpighii or mucosum. Haddon[64] found the pigment quite as plentiful in the corium as in the stratum mucosum of the buccal mucous membrane.

Tizzoni,[65] in the pigmentation produced experimentally in the buccal mucosa of rabbits, found pigmented carrier cells in the corium, and pigment in the deeper layers of the stratum mucosum.

Dixon Mann[66] draws a sharp distinction between pigmentation of the mucous membrane and that of the skin. Pigmentation of mucous membrane is not general; it requires certain local conditions (friction, local hyperæmia) for its development, and the pigment has a different histological site. The corium contains pigmented carrier cells, as is the case in the skin, but the stratum mucosum contains no pigment, possibly because the cells composing it do not have the finger-like processes [67] which in the skin are thought to receive the pigment from the carrier cells. When, exceptionally, pigment was found in the stratum mucosum it was seen to be not in, but between, the cells.

Pigmentation of Serous Membranes.—Addison[68] described discrete pigmentation of the peritoneum in one of his cases, and a similar case is mentioned by Dr. Wilks.[69] Dixon Mann[70] has described the same appearance; the intestines are described as being otherwise normal, and no mention is made of any old peritonitis or tuberculosis.

Dr. Greenhow[71] records a case of Addison's disease with pigmented tubercle of the peritoneum, accompanied by signs of past peritonitis. The same writer also quotes[72] a case recorded by Van Andel of pigmentation of the peritoneum, but no mention is made of the presence or absence of tubercle or of past peritonitis. As its occurrence is so rare, it is probable that when present pigmentation is due to past inflammation, and probably of a tuberculous character of the peritoneum. No instance of similar pigmentation in the pericardium or in synovial membranes has been recorded. The marked pigmentation of the pia mater observed by the late Dr. Carrington[73] seems to be unique, and might possibly have been due to the melanæmia of ague.

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[61] Dixon Mann, *Lancet*, April 4, 1891.

[62] Leva, *Virchow's Archiv*, cxxv, p. 35.

[63] *Vide* Plate ii, Croonian Lectures.

[64] *Path. Trans.* 1885, p. 438.

[65] Tizzoni, *Zeigler's Beiträge*, 1889, p. 29.

[66] *Lancet*, April 4th, 1891, p. 766.

[67] Ehrmann, *Wien. allge. med. Zeitung*, 1894.

[68] *Memoir*, p. 37.

[69] *Guy's Hospital Reports*, 1862, p. 56.

[70] *Lancet*, March 21st, 1891, p. 653.

[71] Croonian Lectures, p. 112.

[72] Croonian Lectures, p. 182.

[73] Quoted in *Fagge's Medicine*, vol. ii, p. 509, 1886.

OTHER ANATOMICAL LESIONS MET WITH IN ADDISON'S DISEASE.

In some of Addison's cases a hypertrophied condition of the lymphoid follicles in the stomach and intestines, as well as some enlargement and softening of the spleen, were noted. The exaggeration of the lymphoid tissue has been frequently noted since, and Dr. Greenhow[74] considered it as one of "the characteristic, though perhaps not quite invariable, lesions" of the disease. There does not appear to have been any diarrhœa in the cases in which this condition was marked. It might, perhaps, be considered that this condition of the lymphatic follicles is to some extent in favour of the view that when the suprarenal bodies are functionless, whether from destruction or atrophy, some toxin is circulating in the body. The occurrence of leucocytosis after the injection of bacterial poisons or even the injection of albumen[75] is presumably accompanied by increased activity of the lymphoid tissue of the organism. In some cases persistence of the thymus gland has been recorded.

A softened condition of the brain with an increased amount of cerebro-spinal fluid has been recorded in some cases[76] of Addison's disease, and was probably accidental, but its occurrence is of interest from the marked inflammatory changes resulting from removal of the suprarenal bodies in animals in Tizzoni's hands.

Tizzoni[77] quotes two cases of Addison's disease in which lesions of the central nervous system were found: 1. Bourredi's case: Caseous change in the suprarenal bodies associated with hyperæmia of the cord, perivascular inflammation, degeneration of nerve fibres, and changes of varying degree in the ganglion cells. 2. Semmola's case: A normal condition of the suprarenal capsules accompanied by mucoid degeneration of the stroma of the abdominal ganglia of the sympathetic and small cell infiltration around the central canal of the spinal cord.

In connection with the view that Addison's disease is of the nature of a toxæmia, it would be natural to expect to find changes corresponding to those described by Bowman[78] in the spinal cord in pernicious anæmia.

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[74] Croonian Lecture, p. 28.

[75] Kanthack and Hardy, *Phil. Trans.*, 1894, p. 293.

[76] *Loc. cit.*, p. 29; Addison, p. 23, 36.

[77] *Ziegler's Beitr.*, vol. vi, p. 9.

[78] *Brain*, 1894, p. 198.

LECTURE III.

EXPLANATION OF ADDISON'S DISEASE: (*a*) NERVOUS THEORY (*b*) THEORY OF SUPRARENAL INADEQUACY; (1) AS EXCRETORY GLANDS, (2) AS SECRETORY GLANDS. TREATMENT OF ADDISON'S DISEASE BY SUPRARENAL EXTRACT.

THE NERVOUS THEORY OF ADDISON'S DISEASE.

THE experimental work of Phillipeaux, Harley, and Tizzoni point to the absence or unimportance of any function on the part of the suprarenal bodies. As already seen this negative view as to the functions of the suprarenal bodies held the field from Addison's discovery until quite recent times. On such a physiological basis the connection between disease of the suprarenal capsules and Addison's disease was explained by the secondary morbid changes, induced by the lesions in the suprarenal bodies, in the neighbouring semilunar ganglia, solar plexus, and sympathetic nerves. This conception will be for ever associated with the name of Dr. Samuel Wilks. It was based on *post-mortem* investigation showing the spread of inflammation from the tuberculous suprarenal bodies to the semilunar ganglia and other branches of the sympathetic.

Dr. Greenhow[1] inferred that at least all the more important features and prominent symptoms of the disease are due to morbid changes in the nerves, the changes in the nerves being (1) irritation and (2) atrophy. The collapse and the extreme state of debility are thus explained as the result of the altered condition of the sympathetic in the abdomen. The vomiting and pigmentation are referred to the direct irritation of the sympathetic by the caseous material in the suprarenal bodies, or from the same cause acting reflexly through the cerebro-spinal system.[2]

The view of Wilks and Greenhow may be summarised thus: The lesion is primary in the suprarenal bodies, and always of the same nature, while the symptoms of the disease aré due to the secondary effect on the adjacent sympathetic, the solar plexus, and semilunar ganglia. Arnaud and Alexais[3] accepted the principle, but by limiting the nervous changes to the ganglia in the fibrous capsule of the adrenal bodies they were able to explain the fact that in Addison's disease the solar plexus and semilunar ganglia may be healthy.

A natural modification of these views is that Addison's disease is due to changes in the abdominal ganglia and sympathetic, which may be due to disease of the suprarenal bodies, but is quite independent of a special, or indeed of any, lesion in them. This theory was supported by

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[1] Croonian Lecture, p. 73.
[2] Croonian Lecture, p. 83.
[3] *Rev. de Méd.*, 1891, p. 366.

Jaccoud, von Kahlden, and others from the clinical and morbid anatomy point of view, and by the experimental researches of Tizzoni. Semmola[4] carried this view to an extreme degree; he believed that not only had changes in the suprarenal bodies nothing to do with Addison's disease, but, when they did exist, that they were trophic lesions due to injury to the nerves which presided over their nutrition.

The nervous theory does not explain the numerous cases recorded of typical Addison's disease, in which special attention has been paid to the condition of the semilunar ganglia and adjacent sympathetic, and in which they have been found to be normal, since continued irritation could not last for any time without setting up inflammatory changes *in situ*. Still less does it explain the occurrence of the symptoms of Addison's disease associated with simple atrophy of the adrenal bodies. Apart from these facts, which by so directly contradicting the data of the theory put it out of court, there are considerable difficulties in the working of the theory. Some of the changes described as responsible for the disease have considerable resemblance to those normally found in adult life, that is, those in the semilunar ganglia. The changes in the sympathetic, etc., according to Greenhow, are (1) irritative in the early stage, followed by (2) atrophic changes corresponding to two stages of the disease. The disease cannot be divided into an early stage showing symptoms the result of a discharging lesion, and a later with symptoms due to an atrophic change in the sympathetic. "Vomiting in advanced cases is seldom absent, and may be spontaneous and irrepressible."[5] Convulsions not uncommonly occur shortly before death, and never in the earlier stage, when according to this view they would naturally be looked for. Pigmentation is nearly always a symptom occurring late in the course of the disease, whereas, according to the view that it is due to irritation of the sympathetic, it should always appear fairly early.

Dr. Bedford Fenwick[6] has suggested that when the medulla of the suprarenal body is affected the constitutional symptoms result, and that when the lesion spreads to the cortex bronzing follows. This would explain the sequence of events, but it would also logically necessitate the constitutional symptoms of Addison's disease appearing whenever the medulla is affected, which is very far from being the case. Experimental removal of the cœliac plexus leads to rapid emaciation, low temperature, diminution in the amount of urea in the urine, acetonuria,[7] though this is disputed,[8] and acetonæmic coma. These results do not support the view that Addison's disease is due to an irritating and destructive lesion of the sympathetic around the suprarenal bodies.

There are numerous examples of slow irritation of the abdominal sympathetic by enlarged glands, spinal caries, surgical and tuberculous kidney, abdominal aneurysm, and chronic peritonitis, where there are no symptoms of Addison's disease, except perhaps some pigmentation. Although it is the sign by which this disease is perhaps most often recognised, the bronzing is not only variable in degree and late in appearing, but is also met with in other diseases, as in exophthalmic goître.

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[4] *Transactions of International Medical Congress*, 1881, vol. ii, p. 71.

[5] Dr. Greenhow, Croonian Lectures, p. 10.

[6] *Path. Trans.*, vol. xxxiii, p. 351; also Alexais and Arnaud, *Rev. de Méd.*, 1891.

[7] Lustig, *Archiv. Ital. de Biolog.*, xii.

[8] Bonone, *Archiv. de Biolog.*, xvii.

Now, since in exophthalmic goître changes in the sympathetic have been described, it might be thought that there are analogies between it and Addison's disease. It may then be well briefly to consider this point. Professor Greenfield[9] in his Bradshaw lecture showed that exophthalmic goître is associated with subacute inflammation of the pons, medulla, and parts of the sympathetic, and ascribed these changes to excess or alteration of the internal secretion of the thyroid gland.

Addison's disease and exophthalmic goître differ very considerably in the clinical picture they present; but they have, though far from constantly, two classes of symptoms in common, namely, gastro-intestinal disturbance and anomalies of pigmentation. Supposing that these common symptoms are both connected with irritation of the nervous system, the conditions are not fairly analogous. For according to the nervous theory of Addison's disease the irritation is simple, and due to the extension of chronic inflammation to the abdominal sympathetic, while in exophthalmic goître the changes and irritation of the nervous system constitute only half the morbid factors present. In addition there is probably a poison present which, independently of the nervous changes it produces, may very well be capable of producing textural lesions and functional disorders. In other words, a consideration of exophthalmic goître does not lend any support to the purely nervous theory of Addison's disease. As has been already seen, the nervous theory is untenable, since the sympathetic in the neighbourhood of the suprarenal bodies is not constantly altered.

THEORY OF SUPRARENAL INADEQUACY.

Since the nervous theory does not explain Addison's disease, the rival theory of suprarenal inadequacy must be examined. This theory assumes that the suprarenal bodies are active glands, and that interference with their functions gives rise to Addison's disease.

Since the morbid symptoms are connected with some change in the constitution of the blood, this theory might, on contradistinction to the nervous theory, be called the chemical theory of Addison's disease.

In the foregoing sketch of the physiology, the suprarenal bodies were shown to be functional glands, but discussion of the nature of this function was postponed. The two views as to their physiology were:

1. That the suprarenal bodies are excretory or katabolic in function. That they pick up and remove from the circulation effete blood pigment and toxic bodies, and destroy them.

2. That these organs are secretory or anabolic. That they manufacture some fluid which passes into the blood vessels or lymphatics, and is of use in the economy.

Before discussing which of these theories is correct, three questions must be considered:

(1) How do the facts of morbid anatomy bear on the hypothesis that Addison's disease is due to the loss of function of the adrenal bodies?

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[9] *Lancet*, December 16th, 1893.

(2) Is the disease likely to be a toxæmia?

(3) Can the symptoms of the disease be explained on this hypothesis?

I.—BEARINGS OF MORBID ANATOMY ON THEORY OF ADRENAL INADEQUACY.

It is known that destructive tuberculous lesions and atrophy of the suprarenal bodies may give rise to the symptoms of Addison's disease.

But the following objections may be raised to the theory of suprarenal inadequacy:—

1. The existence of cases where *post mortem* the suprarenal bodies are found to be extensively destroyed by tubercle or new growth, and in which definite clinical symptoms of Addison's disease have been absent during life. 2. Secondly, that there are cases clinically of Addison's disease in which *post-mortem* caseation of comparatively small amount is found in the suprarenal capsules—perhaps only in one—and in which the amount of damage is even less than in cases which have presented no sign of Addison's disease. Since a comparatively small part of the available suprarenal substance is thus rendered functionless, it has been argued that the concomitant symptoms cannot be due to abolition of the function of the organs. And (3), lastly, that there are examples of Addison's disease in which the suprarenal capsules themselves are healthy, though the surrounding sympathetic nerve plexuses and semilunar ganglia are involved in dense adhesions or by a growth, such as lymphadenoma.

In reply to these the following considerations may be brought forward:

1. In cases where the organs are extensively destroyed by tubercle or invaded by new growth the absence of symptoms may be explained in two ways: (*a*) The change in the adrenal bodies is usually a secondary result of advanced disease in other organs, which has killed the patient before the symptoms of Addison's disease, usually a chronic affection, have had time to develop. (*b*) That some compensation for the destruction of the suprarenal glands is present in accessory suprarenal bodies, and that, as in the case of the thyroid gland, symptoms due to the destruction of the main glands are thus avoided.

2. In reply to the objection that when the lesion of the suprarenal substance is not of considerable amount the remaining part of the organ, if healthy, should produce compensation, and thus prevent the development of symptoms, it may be urged that failure in this power of compensation may be due to inherent want of vitality, to concomitant atrophy, or possibly—and this is a point requiring investigation—to the tuberculous growth interfering with the efferent vessels. The common tuberculous caseous change always begins in the medulla, and thus might easily obstruct the vascular connections of the organ, and so render it functionless, even though there was a sufficiency of secreting gland tissue left.

3. In the few cases of Addison's disease, where the suprarenal bodies are described as healthy, while the sympathetic and semilunar ganglia were involved in dense adhesions or in a growth, it is possible that the vessels and lymphatics of the suprarenal capsules were thus interfered with, and so the

organs were placed outside the circulation and rendered functionless. The sequence of events, then, may be compared to Bòinet's experimental ligature of the pedicle (and veins) of the suprarenal bodies, with its resulting fatal toxic effects. Hence it may be concluded that obstruction to the efferent vessels of the suprarenal capsules is quite a possible cause of Addison's disease. The facts of morbid anatomy, then, appear to be compatible with the view that Addison's disease can be explained by suprarenal inadequacy.

II.—IS ADDISON'S DISEASE LIKELY TO BE A CHRONIC TOXÆMIA?

Addison's disease and myxœdema are in many ways analogous. The destruction of the thyroid gland or its experimental removal leads to a train of symptoms—myxœdema—which can be satisfactorily obviated by artificially supplying the organism with the extract of the thyroid. The same is probably true of the suprarenal bodies.

In myxœdema the cause of the symptoms might be (1) a toxic condition of the blood due to the suspended secretion of the thyroid gland, or (2) a condition of general apathy of the nervous system from the absence of its normal stimulus provided by the secretion of the thyroid gland.

According to the general view myxœdema is due to the absence of thyroid secretion causing a loss of functional activity on the part of the tissues, on which, in all probability, the accumulation of mucin depends. Possibly some toxic body accumulates in a similar manner to mucin, and exerts a poisonous action on the central nervous system. In support of this the toxicity of the urine has been found to be increased by thyroidectomy, the curve of the toxicity varying with the morbid symptoms.[10] In experimental removal of the suprarenal bodies the blood acquires a toxic property, as shown by its effect on other animals.[11]

The extreme debility and languor of Addison's disease, with the periodic exacerbations in the progress of the disease, are very like the same events in pernicious anæmia. The phenomena of pernicious anæmia are best explained by the view that absorption of toxic bodies occurs in the portal system.

Addison's disease and uræmia present certain analogies. In both there is a combination of symptoms suggesting paralysing and irritating factors at work—the drowsiness and not infrequent paralysis of uræmia and the extreme languor and occasional convulsions before death in Addison's disease.

Bouchard has found that in normal urine there are seven toxic bodies. In uræmia these poisons are retained in the body, and the urine is harmless. Now in Addison's disease, since the kidneys are nearly always healthy, the toxic bodies need not be retained in the body, and so might be found in the urine. It is therefore a point urgently requiring investigation as to whether the urine in Addison's disease is more toxic than in health, and what are the results obtained by injecting it into animals as compared with Bouchard's results with healthy urine. The solution of this problem would go far to settle the question whether Addison's disease is a chronic toxæmia.

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[10] Masoin, *Compt. Rend. Soc. de Biolog.*, February 3rd, 1894.

[11] Abelous and Langlois, *loc. cit.*

Quite recently Schäfer and Oliver[12] have found that extracts from the urine of patients with Addison's disease, when injected into animals, have the same effect as normal urine. This observation they regard as being important evidence that the suprarenal bodies do not excrete poisons, but it also militates against the view that Addison's disease is a toxæmia.

From analogy and from the toxic condition of the blood in animals deprived of their suprarenal bodies it would seem probable that Addison's disease is a toxic condition, but the absence of special toxic bodies from the urine is strongly against this view. Further experiments are required, and for the present the question as to whether Addison's disease is or is not a toxic condition should be left open.

III.—ON THE ASSUMPTION THAT ADDISON'S DISEASE MIGHT BE A CHRONIC TOXÆMIA, CAN ITS SYMPTOMS BE EXPLAINED ON SUCH A HYPOTHESIS?

The extreme debility might be due to a toxin possessed of properties like those of curare. Since, however, suprarenal extract has marked toxic effects, it might well be argued that its absence fully accounted for the extreme debility and languor of Addison's disease, and that it was quite unnecessary to invoke a hypothetical toxin for this purpose. Experimentally, however, the injection of blood from acapsulated animals into others gives rise to a temporary condition of extreme languor; so it is not unreasonable to consider this phenomenon in the human subject as possibly due to the presence of a toxin having an action like that of curare.

The gastro-intestinal symptoms might well be due to the effects of a toxin exerting an irritating effect on the central and visceral nervous systems. Pigmentation might be the result of the constant influence of a toxic substance on the sympathetic nervous system. A similar explanation accounts for pigmentation in exophthalmic goître. The influence of the nervous system on pigmentation of the skin, though not proved physiologically, is extremely probable from clinical observations.

The increased pigmentation is an exaggeration of the normal, and the influence of the sympathetic is probably exerted by altering the condition of the vessel wall, and so allowing increased transference of pigment by the carrier cells to the epidermis. But it must be remembered that there is the hypothesis that stimulation of the sympathetic nerve fibres increases an active formation of pigment by the cells of the stratum Malpighii. The existence of chromatogenic nerve fibres[13] has been suggested, but cannot be considered to have been proved.

The extreme debility may be considered either as a result of a toxic condition or as a state of atony due to the absence of a necessary stimulus. The vomiting, gastro-intestinal disturbances, and pigmentation point to there being some positive irritation rather than to a mere absence of a normal stimulus. On the whole, the symptoms of Addison's disease are better explained as the result of a toxæmia than on the supposition that they are solely due to the absence of the stimulus normally provided by the internal secretion of the adrenals to the body generally.

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[12] *Proc. Physiol. Soc.*, March 16th, 1895.

[13] Baumel, *Académie de Médecine de Montpellier*, 1889; quoted by Guay, Thèse pour le Doctorat, Paris, 1893.

Having seen that the facts of morbid anatomy are compatible with the view that Addison's disease is due to inadequacy of the suprarenal bodies, and that it is an open question whether Addison's disease is due to a toxic or to an atonic condition, let us examine the two theories as to the function of the suprarenal bodies.

The Theory that the Suprarenal Bodies Remove Pigment and Toxic Substances from the Blood.

What evidence is there that blood pigment undergoes any change in the suprarenal bodies?

The hæmoglobin is freed from the red blood corpuscles chiefly in the spleen, and possibly to some extent in the red marrow of bone,[14] but the former is the important seat of this change, otherwise hæmoglobin would appear in the urine. The katabolic changes undergone by hæmoglobin take place in the liver.[14]

MacMunn's view is that the suprarenal capsules perform this function, and that when they are destroyed an accumulation of effete pigment occurs in the circulation. No such accumulation of solid pigment has ever been found in the blood in Addison's disease. Brown-Séquard and Boinet are the only observers who have ever recorded pigment granules in the blood after experimental removal of the suprarenal capsules. In animals killed by toluylene diamine, Pilliett[15] noticed products of blood destruction in the medulla of the suprarenal capsules giving rise to pigmentation, but this poison produces hæmolysis so freely that this observation lends no support to the view that normally any changes occur in the medulla of the suprarenal bodies.

But it might be argued that, even if there is no solid pigment free in the blood, there might be an increased amount of soluble pigment or chromogens in the circulation as the result of destruction of, or interference with, the suprarenal capsules. Such an excess of soluble pigment might be thought to provide the cells of the stratum Malpighii with satisfactory pabulum for pigment formation. But such soluble pigment should pass freely into the urine. Is there any evidence of such increase of urinary pigments in Addison's disease? Thudichum,[16] in a continuous examination for sixty-five days of the urine of a case of Addison's disease found a deficiency in the colouring matters. A similar result was obtained by Dr. A. E. Garrod, who most kindly made some analyses of the urine of a case of Addison's disease for me, and by Dixon Mann.[17]

MacMunn based his theory on the belief that hæmoglobin and histohæmatins become changed into hæmochromogen, histohæmatins being found by him in the cortex, and hæmochromogen in the medulla of the suprarenal capsule. Hæmochromogen, according to this author, is blood pigment in an excretory stage, and is also found in the bile. In Addison's disease the interference with this pigment-metabolising function of the suprarenal bodies was shown hy the presence of a pigment, urohæmatoporphyrin, in the urine. He found this body, however, in the urine of diseases such as enteric fever, measles, cirrhosis, meningitis,[18] etc., in which the suprarenal capsules are not specially affected. In addition it has been shown that urohæmatoporphyrin is not a definite chemical compound, but a mixture of a larger quantity of hæmatoporphyrin and a smaller quantity of urobilin,[19] both of which are among the normal urinary pigments.[20] Garrod[21] has found hæmatoporphyrin in considerable quantities in the urine of tuberculous subjects, and, since Addison's disease is usually tuberculous, an increased amount of hæmatoporphyrin, if present, would be thus accounted for.

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[14] Foster, *Physiology*, part ii, p. 747, 1889; Wm. Hunter, *Lancet*, vol. ii, 1888.

[15] *Compt. Rend. Soc. de Biolog.*, February 3rd, 1894.

[16] The Report of Medical Officer to Privy Council, 1868.

[17] *Lancet*, 1891, April 4th.

As shown above, the urinary pigments are not increased in Addison's disease, and hæmatoporphyrin in the analysis Garrod kindly did for me was only present as a trace. Even if hæmatoporphyrin were present uniformly in large quantities in Addison's disease this would prove little, since it has been shown to occur in considerable amounts in such various conditions and diseases as sulphonal poisoning,[22] gout,[23] chorea,[24] phthisis, and pneumonia, and not to be increased in pernicious anæmia. Indican has been found in the urine in increased quantities in Addison's disease, but its presence is a sign of intestinal disturbance, and points possibly to an auto-intoxication, but not to any change in metabolism of the pigments of the blood. From these considerations it appears highly improbable that the suprarenal bodies have any action on the effete pigments of the blood.

What evidence is there that in the suprarenal capsules poisonous bodies are destroyed or rendered innocuous? On removal of these organs the animals die, and their blood, when injected into healthy animals, gives rise to symptoms resembling those seen after removal. This toxic property of the blood might be due to non-excretion on the part of the suprarenal bodies, or to their internal secretion no longer neutralising this toxic property of the blood.

Now, Tizzoni[25] and Nothnagel[26] crushed the suprarenals, and left them to be absorbed *in situ*, without any signs of toxæmia resulting. If, therefore, the former alternative be set up as a hypothesis, at any rate the suprarenal bodies do not contain the poisonous substances which they might be supposed to remove. This same hypothesis is further opposed by the experiments of Abelous and Langlois.[27] They showed that the toxæmia due to ablation of the organs can be counteracted by injection of suprarenal extract. Now, if the suprarenal bodies excreted a poison, which when accumulating in the blood gives rise to toxic symptoms, injection of suprarenal extract would only increase these toxic effects.

These two observations, then, are both opposed to the hypothesis that the suprarenal bodies excrete a poisonous substance. On the other hand, it is known[28] that injection of very large quantities of suprarenal extract, equal to several times the weight of the suprarenal bodies, produces death.

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[18] *Journal of Physiology*, vol. x, 1889.

[19] Le Nobel, *Pflüger's Archiv*, 1887, vol. xi, p. 501; Garrod, *Journal of Physiology*, vol. xiii, 1892, p. 598; Zoga, *Archiv. Ital. di Clinic. Medic.*, 1893; G. Hopkins, *Guy's Hospital Reports*, vol. l, p. 393, 1893.

[20] Garrod, *Journal of Physiology*, vol. xvii, 1894, p. 349.

[21] Garrod, *Journal of Path.*, vol. i, p. 194.

[22] Salkowski, *Zeit. physiol. Chem.*, 1891, vol. xv, 286; Percy Smith, *St. Thomas's Hosp. Reports*, vol. xxi.

[23] Garrod, *Journal of Pathology*, vol. i, p. 194.

[24] *Loc. cit.* [25] *Loc. cit.* [26] *Loc. cit.* [27] *Loc. cit.*

[28] Oliver and Schäfer, *loc. cit.*

At first sight this might seem to tend in the opposite direction, but it does not really do so. It only proves that an abnormal and poisonous dose of suprarenal extract or secretion has been used.

Again, Abelous and Langlois[29] showed that after removal of the suprarenal bodies a toxic body with properties like curare appeared in the blood. But, on the other hand, Schäfer and Oliver found that the effect of suprarenal extract was not at all comparable to that of curare.

These two experiments are not contradictory; they only show that the body or bodies extracted from the suprarenal capsules are not the same as those present in the blood of animals whose adrenals have been removed. This is a strong argument against the theory that the suprarenal bodies are excretory glands.

There is, then, evidence, that the suprarenal bodies do not remove effete blood pigment from the blood or absorb toxic bodies and render them harmless.

THEORY THAT ADDISON'S DISEASE IS DUE TO AN INADEQUATE SECRETION ON THE PART OF THE SUPRARENAL BODIES.

Since the function of the suprarenal bodies is not excretory we are left with the alternative view that they are secretory glands providing an internal secretion like the thyroid. The researches of Abelous and Langlois[30] and of Schäfer and Oliver[31] form the basis for this belief.

* Schäfer and Oliver[32] lately showed that healthy human suprarenal capsules yield a powerful extract, but that in cases of Addison's disease no active extract can be obtained. This points strongly to the conclusion that Addison's disease is due to arrest of secretion of the suprarenal bodies.

In seeking for an explanation of the phenomena of Addison's disease in a cessation of the secretory function of the suprarenal bodies the next step is to inquire whether the facts available point (1) to this secretion directly antagonising a poison which is continually being formed in the body. This antagonism might be conceived of (*a*) as occurring in a manner analogous to the neutralisation of an acid by an alkali, or (*b*) as being due to the secretion exerting a ferment-like action on these hypothetical toxins and destroying them. Or (2) to the secretion acting as a stimulus to the various tissues of the body. This tonic effect on the tissues might act conceivably in three ways: (*a*) by regulating their nutrition and activity; in the absence of this restraining influence, the tissues, so to speak, run riot, and might even produce toxic bodies.[33] (*b*) By increasing the resistance and defensive powers of the cells of the body, including the white blood corpuscles, so that they are able to withstand the poisonous bodies possibly resulting from the general metabolism of the body, and to destroy them. (*c*) By increasing their functional activity without any reference to the presence of toxic bodies.

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[29] *Loc. cit.* [30] *Loc. cit.* [31] *Loc. cit.*

* I take this opportunity of thanking them for the generous manner with which they have put me in possession of the contents of their communication to the Physiological Society on March 16th, 1895, before the publication of that paper.

[32] *Proc. Physiol. Society*, March 16th.

[33] Thiroloix, *loc. cit.*

Schäfer and Oliver's[34] experiments show that suprarenal extract has a very definite effect on healthy animals, being among other things, a powerful vascular tonic. This observation proves that the secretion is not merely a chemical antidote.

In order to prove whether suprarenal extract or secretion has any such neutralising action on the toxic bodies in the blood of animals deprived of their suprarenal bodies, experiments should be performed on the lines of Buchner's[35] experiment with antitoxin. Guinea-pigs are twenty times more susceptible to tetanus than white mice. A mixture of tetanus toxin and antitoxin was prepared so that no effect followed its injection into white mice, but when tried on guinea-pigs a fatal result was produced. So the immunity conferred by antitoxin is not due to a mere neutralisation, but to the effects of antitoxins on the tissues. Suprarenal extract should, like antitoxin, be mixed with toxic blood from animals dying from ablation of the suprarenal bodies, and the point be settled whether the amount of suprarenal extract required to counteract the accompanying toxins is the same for all animals, in which case it would appear to be a process of neutralisation, or whether it varies with the susceptibility of different animals.

With regard to the possibility of the suprarenal extract containing a ferment which destroys hypothetical toxins in the blood, it must be borne in mind that such a ferment would be destroyed by boiling. One of the extracts employed by Schäfer and Oliver was made with boiling water. Mere boiling does not affect the action of the extract, but continued boiling abolishes its activity. It is probable, therefore, that the active principle is not of the nature of a ferment; its action is not limited to the neutralisation of a poison in the blood. It certainly has direct stimulating powers on the tissues, as shown by Schäfer's and Oliver's experiments. It is tempting to jump to the conclusion that its curative properties are due to stimulation of the tissues, including the white corpuscles, and to increased defensive activity on their part; but at the present time there is not enough evidence to warrant any definite opinion.

To sum up, Addison's disease is due to an inadequate supply of suprarenal secretion. Whether the deficiency in this internal secretion leads to a toxic condition of the blood, or to a general atony and apathy, is a question which must remain open.

TREATMENT.

In conclusion, a few words about the treatment of Addison's disease by suprarenal extract will not be out of place, since such a course of treatment is the logical outcome of a belief in the view that Addison's disease is due to an absence of the internal secretion of the suprarenal bodies. But few observations have been published. Dr. G. Oliver[36] treated two cases for three months with suprarenal extract by the mouth; they improved, in that they gained weight, became less pigmented, and were freed from nausea and anorexia.

I have had a woman with Addison's disease under treatment at St. George's Hospital since June, 1894. She is stronger

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[4] *Loc. cit.*

[35] *Münchener med. Wochenschrift*, 1893, Nos. 24, 25.

[36] *Pulse Gauging*, p. 89.

and less subject to nausea and vomiting since taking suprarenal extract by the mouth; and though still pigmented is on the whole decidedly better. The quantity of the extract that should be given is a point which it is important to ascertain, otherwise disappointment may result because inadequate doses are employed; a dose equal to 45 grains of the original gland spread over the twenty-four hours is certainly not too much. Since each suprarenal capsule of a man weighs about 1 drachm, and since the medulla is the only part containing the active principle, this dose is nearly equal to two suprarenal bodies a day.

Dr. T. Oliver[37] mentions hypodermic injections of suprarenal extract; but the treatment was not given a fair trial, as the patient did not remain under observation. A more extended course of subcutaneous injection by Chauffard[38] was also unsuccessful.

Sir D. Duckworth, in an article in the *Encyclopædia of Medicine*, New York—the proofs of which he has most kindly allowed me to see—quotes a case of Sir T. Grainger Stewart's, in which feeding with the suprarenal bodies produced no good effect.

Dr. G. Oliver's and Professor Schäfer's physiological experiments suggested the use of the extract as a hæmostatic agent. The remedy is on its trial, and will probably, like thyroid-extract, be found to be useful in diseases other than that for which it was first employed.

Since the action of suprarenal extract on the vascular system is the reverse of that of thyroid extract, Dr. G. Oliver has suggested its use in exophthalmic goître. Inasmuch as the extract has such an extreme power of constricting the vessels, Dr. Oliver thinks it may be useful as a hæmostatic in purpura, hæmophilia, etc., and in the various conditions of vasomotor relaxation and paresis, such as occur at the menopause, in "cyclic" albuminuria, and in diabetes.[39] Possibly it might be useful in cases of shock and collapse. Dr. Douglas Stanley[40] has found that it increases the number of red blood corpuscles in pernicious anæmia. Oliver and Schäfer[41] have found that suprarenal extract is not damaged by artificial gastric digestion, so that giving the drug by the mouth is physiologically correct.

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[37] *International Clinics*, 1895, vol. ii, series 4, p. 23.

[38] *Medical Week*, February, 1894, p. 85.

[39] *Pulse Gauging*, p. 90.

[40] BRITISH MEDICAL JOURNAL, February 16th, 1895, p. 370.

[41] *Proc. Physiol. Soc.*, March 16th, 1895.

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